

CLINICAL CAPSULES

Amoxicillin and GAS Pharyngitis

Amoxicillin given once daily to treat group A streptococcal pharyngitis was no less effective than a twice-daily dose, based on data from 652 children seen in a private pediatric practice during a 2-year period.

Although once-daily penicillin has less effectiveness against group A streptococcal (GAS) pharyngitis than twice-daily dosing, the researchers proposed that amoxicillin, with its longer serum half-life, might be just as effective in one daily dose as in two daily doses, which could improve adherence in some cases.

Dr. Herbert W. Clegg, a pediatrician in group practice in Charlotte, N.C., and his colleagues recruited children aged 3-18 years with signs and symptoms of GAS pharyngitis. The children were randomized to a once-daily dose of either 750 or 1,000 mg or a twice-daily dose of 375 or 500 mg, depending on the child's weight. The treatment duration was 10 days for both groups, and patient demographics and compliance with therapy were similar in both groups.

The researchers assessed bacteriologic failure rates based on pharyngeal swabs

taken at 14-21 days (visit 2) and 28-35 days (visit 3) after the start of treatment (*Pediatr. Infect. Dis. J.* 2006;25:761-7).

Not all children returned for visits 2 and 3 for various reasons, but the bacteriologic failure rate was 33% for both groups in an intent-to-treat analysis that included all patients, the researchers noted. The rates between the groups were not significantly different on further analysis.

Failure rates at visit 2 were 20% (59 of 294) in the once-daily group vs. 16% (46 of 296) in the twice-daily group. Failure rates at visit 3 were 3% (6 of 216) in the once-daily group vs. 7% (16 of 225) in the twice-daily group.

Xopenex HFA[™]

(levalbuterol tartrate) Inhalation Aerosol

FOR ORAL INHALATION ONLY

BRIEF SUMMARY

INDICATIONS AND USAGE

XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease.

CONTRAINDICATIONS

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

WARNINGS

1. Paradoxical Bronchospasm: Like other inhaled beta-adrenergic agonists, XOPENEX HFA Inhalation Aerosol can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister. **2. Deterioration of Asthma:** Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of XOPENEX HFA Inhalation Aerosol than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

3. Use of Anti-Inflammatory Agents: The use of a beta-adrenergic agonist alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen. **4. Cardiovascular Effects:** XOPENEX HFA Inhalation Aerosol, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients, as measured by heart rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of XOPENEX HFA Inhalation Aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, XOPENEX HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. **5. Do Not Exceed Recommended Dose:** Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected. **6. Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions may occur after administration of racemic albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving XOPENEX HFA Inhalation Aerosol.

PRECAUTIONS

General

XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after the use of any beta-adrenergic bronchodilator.

Large doses of intravenous racemic albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-adrenergic agonist medications, XOPENEX HFA Inhalation Aerosol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

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Information for Patients

The action of XOPENEX HFA Inhalation Aerosol should last for 4 to 6 hours. XOPENEX HFA Inhalation Aerosol should not be used more frequently than recommended. Do not increase the dose or frequency of doses of XOPENEX HFA Inhalation Aerosol without consulting your physician. If you find that treatment with XOPENEX HFA Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using XOPENEX HFA Inhalation Aerosol, other inhaled drugs and asthma medications should be taken only as directed by your physician.

Common adverse effects of treatment with inhaled beta-agonists include palpitations, chest pain, rapid heart rate, tremor, and nervousness. If you are pregnant or nursing, contact your physician about use of XOPENEX HFA Inhalation Aerosol. Effective and safe use of XOPENEX HFA Inhalation Aerosol includes an understanding of the way that it should be administered.

Use XOPENEX HFA Inhalation Aerosol only with the actuator supplied with the product. Discard the canister after 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 Inhalation Aerosol to children is similar to that for adults. Children should use XOPENEX HFA Inhalation Aerosol under adult supervision, as instructed by the patient's physician.

Drug Interactions

Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should be used with caution with XOPENEX HFA Inhalation Aerosol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

1. Beta-blockers: Beta-adrenergic receptor-blocking agents not only block the pulmonary effect of beta-adrenergic agonists, such as XOPENEX HFA Inhalation Aerosol, 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. **2. Diuretics:** The ECG changes and/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. **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 Inhalation Aerosol 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 Inhalation Aerosol. **4. Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:** XOPENEX HFA Inhalation Aerosol 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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility No carcinogenesis or impairment of fertility studies have been carried out with levalbuterol tartrate. However, racemic albuterol sulfate has been evaluated for its carcinogenic potential and ability to impair fertility.

In a 2-year study in Sprague-Dawley rats, racemic albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at, and above, dietary doses of 2 mg/kg/day (approximately 30 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis and approximately 15 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m² basis). In another study, this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg/day (approximately 3800 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis and approximately 1800 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m² basis). In a 22-month study in the Golden hamster, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg/day (approximately 500 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis and approximately 240 times the maximum recommended daily inhalation dose 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 negative in an *in vitro* chromosomal aberration assay in CHO cell cultures.

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 maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis).

Teratogenic Effects - Pregnancy Category C A reproduction study in New Zealand White rabbits demonstrated that levalbuterol HCl was not teratogenic when administered orally at doses up to 25 mg/kg/day (approximately 750 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis).

However, racemic albuterol sulfate has been shown to be teratogenic in mice and rabbits. A study in CD-1 mice given racemic albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at a 0.25 mg/kg/day (approximately 2 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg/day (approximately 20 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg/day (less than the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg/day of isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when racemic albuterol sulfate was administered orally at a dose of 50 mg/kg/day (approximately 1500 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis).

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.

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

During marketing experience of racemic albuterol, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with racemic

albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between racemic albuterol use and congenital anomalies has not been established.

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

Tocolysis XOPENEX HFA Inhalation Aerosol has not been approved for the management of preterm labor. The benefit:risk ratio when levalbuterol tartrate is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta2-agonists, including racemic albuterol.

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 HFA Inhalation Aerosol 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 HFA Inhalation Aerosol is administered to a nursing woman.

Pediatrics The safety and efficacy of XOPENEX HFA Inhalation Aerosol have been established in pediatric patients 4 years of age and older in an adequate and well-controlled clinical trial. Use of XOPENEX HFA Inhalation Aerosol in children is also supported by evidence from adequate and well-controlled studies of XOPENEX HFA Inhalation Aerosol in adults, considering that the pathophysiology, systemic exposure of the drug, and clinical profile in pediatric and adult patients are substantially similar. Safety and effectiveness of XOPENEX HFA Inhalation Aerosol in pediatric patients below the age of 4 years have not been established.

Geriatrics Clinical studies of XOPENEX HFA Inhalation Aerosol did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant diseases or other drug therapy. 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.

ADVERSE REACTIONS 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 in 748 adult and adolescent patients with asthma that compared XOPENEX HFA Inhalation Aerosol, a marketed albuterol HFA inhaler, and an HFA-134a placebo inhaler. The following lists the incidence (% XOPENEX HFA 90 mcg, marketed albuterol HFA inhaler 180 mcg, placebo, respectively) of all adverse events (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 Inhalation Aerosol and more frequently than in the HFA-134a placebo inhaler group. **Body as a whole:** pain (4.0%, 3.4%, 3.6%). **Central nervous system:** dizziness (2.7%, 0.6%, 1.8%). **Respiratory system:** asthma (9.4%, 7.3%, 6.0%), pharyngitis (7.9%, 2.2%, 2.4%), rhinitis (7.4%, 2.2%, 3.0%).

Adverse events reported by less than 2% and at least 2 or more of the adolescent and adult patients receiving XOPENEX HFA Inhalation Aerosol 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, hematuria, and vaginal moniliasis. There were no significant laboratory abnormalities observed in these studies.

Adverse event information concerning XOPENEX HFA Inhalation Aerosol in children is derived from a 4-week, randomized, double-blind trial of XOPENEX HFA Inhalation Aerosol, a marketed albuterol HFA inhaler, and an HFA-134a placebo inhaler in 150 children aged 4 to 11 years with asthma. The following lists the adverse events (% XOPENEX HFA 90 mcg, marketed albuterol HFA inhaler 180 mcg, placebo, respectively) reported for XOPENEX HFA Inhalation Aerosol in children at a rate of 2% or greater and more frequently than for placebo. **Body as a whole:** accidental injury (9.2%, 10.3%, 5.7%). **Digestive system:** vomiting (10.5%, 7.7%, 5.7%). **Respiratory system:** bronchitis (2.6%, 0%, 0%), pharyngitis (6.6%, 12.8%, 5.7%).

The incidence of systemic beta-adrenergic adverse effects (e.g., tremor, nervousness) was low and comparable across all treatment groups, including placebo.

Postmarketing In addition to the adverse events reported in clinical trials, the following adverse events have been observed in postapproval use of levalbuterol inhalation solution. 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, dyspnea, nausea, nervousness, rash, tachycardia, tremor, urticaria. Because these events have been reported spontaneously from a population of unknown size, estimates of frequency cannot be made.

In addition, XOPENEX HFA Inhalation Aerosol, 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.

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Pertussis Booster May Be Needed

Children may need a booster dose of the acellular pertussis vaccine between the ages of 5 and 7 years to ensure protection from illness, according to data from a 7-year population-based study.

A total of 1,293 cases of culture-confirmed pertussis were seen in Swedish children born in 1996 or later during the period from October 1997 to September 2004—after the introduction and widespread use of an acellular pertussis vaccine in Sweden, reported Lennart Gustafsson, Ph.D., of the Swedish Institute for Infectious Disease Control in Solna, and his colleagues (*Pediatrics* 2006;118:978-84).

Overall, 516 cases of pertussis occurred in unvaccinated children (225 per 100,000 person-years in children aged 2 months and younger). But the reported incidence of pertussis dropped significantly after the second and third doses of vaccine. The incidence was 31 per 100,000 person-years between dose two and dose three, and 8 per 100,000 person-years in fully vaccinated children within a year of the third dose (children aged 2 years and younger).

The incidence at 6 years among vaccinated children who had received at least two doses was similar to the incidence shortly after the second dose at ages 5-12 months (32 per 100,000 person-years vs. 31 per 100,000 person-years). But the incidence had increased to 48 per 100,000 person-years in children aged 7-8 years, which suggests a waning of vaccine protection after 6-7 years, the researchers said.

Infant Flu Vaccination Rates Are Low

Only 7.4% and 17.5% of children aged 6-23 months received at least one dose of the influenza vaccine during 2002-2003 and 2003-2004, respectively, based on a representative sample of 13,881 children from the 2003 and 2004 National Immunization Surveys.

The 2002-2003 and 2003-2004 seasons were the first two flu seasons in which vaccination was encouraged, but not formally recommended, for children aged 6-23 months, and more work is needed to ensure at least two doses for previously unvaccinated children in this age group, said Tammy A. Santibanez, Ph.D., and her colleagues at the Centers for Disease Control and Prevention in Atlanta.

Of the children who received at least one dose of flu vaccine, about 40% and 52% went on to be fully vaccinated during the 2002-2003 and 2003-2004 seasons, respectively. Overall, 4.4% and 8.4% of children aged 6-23 months were fully vaccinated during these two seasons.

“Receipt of two doses for previously unvaccinated children is paramount, because receipt of only one dose may provide little to no protection,” the researchers said.

Vaccination rates were significantly lower among children living below the poverty level, non-Hispanic black children, and children with less-educated mothers (*Pediatrics* 2006;118:1167-75). Receipt of at least one vaccination was significantly associated with white or Asian race, younger age at the start of flu season, and vaccine receipt at a private practice or a hospital, after controlling for multiple demographic variables.

—Heidi Splette