CLINICAL CAPSULES

Imaging Agent Tied to Complications

Palatin Technologies, manufacturer of NeutroSpec, is voluntarily suspending U.S. sales and marketing of the radiodiagnostic agent, according to a public health advisory issued by the Food and Drug Administration. The action was taken "pending review of reported and serious life-threatening adverse events associated with use of the product," the FDA said.

NeutroSpec [Technetium (99m Tc) fanolesomab], a murine IgM monoclonal antibody labeled with technetium, is approved for scintigraphic imaging of patients 5 years of age or older with equivocal signs and symptoms of appendicitis.

Two deaths attributed to cardiopulmonary failure within 30 minutes of injection have been reported, as have serious events including cardiac arrest, hypoxia, dyspnea, and hypotension. Most of the adverse events occurred within minutes of injection and required patient resuscitation with fluids, vasopressors, and oxygen. Most of the reports involved patients receiving NeutroSpec for unapproved indications, but "some patients who received the drug for [diagnosis of appendicitis] developed reactions of a similar nature," the FDA said.

The FDA advisory recommended that health care providers discontinue use of NeutroSpec and contact the manufacturer about returning existing stocks.

Any patient given NeutroSpec despite the warning should be closely monitored for at least 1 hour, with access to resuscitation equipment and trained personnel. Patients with underlying cardiopulmonary conditions may be at higher risk for serious complications, the FDA said.

Adverse events can be reported to the manufacturer or directly to the FDA MedWatch reporting system by calling 800-332-1088 or by faxing 800-332-0178.

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.

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/m^2 basis and approximately 15 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m^2 basis). In another study, this effect was blocked by the coadministration of propranolol, a nonselective 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/m^2 basis and approximately 1800 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m^2 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/m^2 basis and approximately 240 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m^2 basis).

Levalbuterol HCl was not mutagenic in the Ames test or the CHO/HPRT Mammalian Forward Gene Mutation Assay.

Levalbuterol HCl was not clastogenic in the in vivo micronucleus test in mouse bone marrow. Racemic albuterol sulfate was 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/m^2 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/m^2 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 0.25 mg/kg/day (approximately 2 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 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/m^2 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/m^2 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/m^2 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.

Rx only.

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Blacks Have Worse Outcomes After ACS

Black patients with acute coronary syndrome face worse angina, physical impairment, and quality of life 1 year later than their white counterparts, reported Dr. John Spertus of Mid America Heart Institute of Saint Luke's Hospital, Kansas City, Mo., and his associates.

Researchers have documented racial disparities in ACS treatment and have found that these disparities have little impact on mortality outcomes. But no studies have assessed racial differences in symptoms, function, or quality of life after ACS treatment, Dr. Spertus and his associates said (J. Am. Coll. Cardiol. 2005:46:1838-44).

They evaluated outcomes using a database on nearly 11,000 consecutive patients treated at two Kansas City hospitals in 2001-2002. At 1-year follow-up, black ACS patients were 46% more likely than whites to have residual angina, and they had more frequent bouts of angina. Blacks also had poorer physical function and worse quality of life than did whites; 52% of blacks reported some degree of limitation, compared with only 29% of whites.

As in previous studies, black patients were much less likely than white patients to undergo primary or secondary percutaneous coronary intervention, to undergo diagnostic angiography, or to have bypass surgery. Yet these treatment disparities did not fully account for the racial differences in outcomes. "Other factors in the care of patients between discharge and 1 year may be responsible," the investigators noted.

Until further research addresses underlying causes, "greater surveillance of the health status of black patients appears warranted so that those who are symptomatic, physically limited, or suffering a significant impairment in their quality of life can be identified and reevaluated for further treatment options," they added.

HCM Diagnosed Later in Women

Hypertrophic cardiomyopathy is diagnosed later in women than in men, and is more likely to progress to severe, disabling symptoms or death, reported Dr. Iacopo Olivotto of Azienda Ospedaliera Universitaria Careggi, Florence, Italy, and associates.

Both findings "underscore the importance of heightened suspicion for HCM in women," the researchers said (J. Am. Coll. Cardiol. 2005;46:480-7).

They assessed disease progression over an average of 6 years in 969 consecutive patients treated for HCM at three medical centers in Italy and the United States. The 393 women were an average of 9 years older than the 576 men at diagnosis. Nearly 60% of the women had severe symptoms, including exertional dyspnea, chest pain, and syncope, compared with fewer than 40% of the men. Women were more likely to have left ventricular outflow obstruction, possibly because of the smaller dimensions of their left ventricular cavities.

Treatment was equivalent for men and women once diagnosed, but women were much more likely to show symptomatic progression and to die from heart failure or embolic stroke. This was due in part to the delay in diagnosis and treatment, but the data suggest that some other, as yet unknown, mechanism related to female gender may make women more prone to HCM progression, the researchers said.

–Mary Ann Moon

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