

POLICY & PRACTICE

Paxil Settlement

The pharmaceutical giant GlaxoSmith-Kline has agreed to settle a class action lawsuit that alleged that the company inappropriately promoted the antidepressant Paxil to children. The \$63.8 million settlement will include any individuals in the United States who bought Paxil or Paxil CR for their minor child. GlaxoSmith-Kline agreed to settle the case in order to avoid "protracted litigation" but officials there believe they acted appropriately, company spokeswoman Mary Anne Rhyné said. The settlement agreement is

expected to receive final court approval in March 2007.

New Children's Ad Guidelines

Advertisers have adopted an updated set of voluntary guidelines that spell out appropriate conduct in advertising to children under age 12. The guidelines were produced by the Children's Advertising Review Unit, which is administered by the Council of Better Business Bureaus and is funded by the children's advertising industry. The guidelines include directives on avoiding deceptive practices, avoiding

misleading product representations and claims, and making disclaimers understandable, and also restrictions on celebrity endorsements, and prohibitions on blurring the line between advertising and program content, among others. For example, the guidelines prohibit the use of program personalities to advertise products or services adjacent to a TV program aimed at children under age 12 in which the same person or character appears. The guidelines also tackle the responsible advertising of food products. Under the guidelines, advertisers depicting food products must show the food in the context of a nutritionally balanced meal and snack

foods should not be shown as substitutes for meals. The voluntary program applies to national advertising directed at children under age 12 years and online data collection targeting children under age 13 years. The guidelines are available at www.caru.org/guidelines/guidelines.pdf.

Misusing Rx Pain Relievers

More people are misusing prescription pain relievers for the first time than are trying marijuana, according to a report from the Substance Abuse and Mental Health Services Administration. About 2.7 million individuals aged 12 years and older reported misuse of prescription pain relievers in the past year, compared with 2.1 million who said they started using marijuana in the last year. The figures are based on the combined results of the 2002 and 2004 National Survey on Drug Use and Health. Overall, marijuana users are still outpacing prescription drug abusers. An annual average of about 11.3 million individuals aged 12 years and older reported using prescription pain medications nonmedically in the past year, compared with an average of 25.5 million individuals who had used marijuana in the past year. "While marijuana continues to be the most commonly used illicit drug, the misuse of prescription drugs is clearly a growing national concern," said Eric Broderick, SAMHSA acting deputy administrator. The report is available online at <http://oas.samhsa.gov/prescription/toc.htm>.

Price Tag for Teen Births

The public cost of teenage births was more than \$9 billion in 2004, according to an estimate of costs to federal, state, and local governments for all births to women aged 19 years and younger prepared by the National Campaign to Prevent Teen Pregnancy. The estimate includes increases in public sector health care costs for the baby, increased child welfare payments and other public assistance, increased costs to state prisons for the children of teen mothers, and lost revenue because of lower taxes paid by parents and the children over their adult lifetimes. The highest costs are for births to mothers 17 years and younger—about \$8.6 billion in 2004. Overall, between 1991 and 2004, the researchers estimate that the public cost of teen births was about \$161 billion.

Investigating SSRIs and Suicide

Officials at the National Institute of Mental Health, part of the National Institutes of Health, are funding new research to help answer questions about the association between selective serotonin reuptake inhibitors (SSRIs) and suicidality. The projects, which will be conducted at academic medical centers across the country, will draw on data from the Food and Drug Administration, the Department of Veterans Affairs, Medicare, and the National Death Index. In one study being conducted at the University of Florida, researchers will examine whether an "activation syndrome" exists among certain young people that is brought on by SSRIs and can lead to suicidality. "These new, multiyear projects will clarify the connection between SSRI use and suicidality," Dr. Thomas Insel, director of the National Institute of Mental Health, said in a statement.

—Mary Ellen Schneider

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR PROAIR™ HFA (ALBUTEROL SULFATE) INHALATION AEROSOL

For Oral Inhalation Only

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION INDICATIONS AND USAGE

PROAIR HFA Inhalation Aerosol is indicated in adults and children 12 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

CONTRAINDICATIONS

PROAIR HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol and any other PROAIR HFA Inhalation Aerosol components.

WARNINGS

Paradoxical Bronchospasm: PROAIR HFA Inhalation Aerosol can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, PROAIR HFA 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.

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 PROAIR HFA Inhalation Aerosol than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

Use of Anti-inflammatory Agents: The use of beta-adrenergic-agonist bronchodilators 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.

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

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.

Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, 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 PROAIR HFA Inhalation Aerosol.

PRECAUTIONS

General

PROAIR HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; 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 use of any beta-adrenergic bronchodilator.

Large doses of intravenous albuterol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. As with other beta-agonists, PROAIR 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

See illustrated Patient's Instructions for Use. Shake well before use. Patients should be given the following information: Prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing three "test sprays" into the air, away from the face.

Keeping the plastic actuator mouthpiece clean is very important to prevent medication build-up and blockage. Wash the mouthpiece, shake to remove excess water, and air dry thoroughly at least once a week. The inhaler may cease to deliver medication if not properly cleaned.

Clean the mouthpiece (with the canister removed) by running warm water through the top and bottom of the mouthpiece for 30 seconds at least once a week. Shake to remove excess water, then air-dry thoroughly (such as overnight). Blockage from medication build-up or improper medication delivery may result from failure to thoroughly air dry the mouthpiece.

If the mouthpiece should become blocked (little or no medication coming out of the mouthpiece), the blockage may be removed by washing as described above.

If it is necessary to use the inhaler before it is completely dry, shake off excess water, replace canister, test spray twice away from face, and take the prescribed dose. After such use, the mouthpiece should be rewashed and allowed to air dry thoroughly.

The action of PROAIR HFA Inhalation Aerosol should last for 4 to 6 hours. Do not use PROAIR HFA Inhalation Aerosol more frequently than recommended. Do not increase the dose or frequency of doses of PROAIR HFA Inhalation Aerosol without consulting your physician. If you find that treatment with PROAIR 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, seek medical attention immediately. While you are taking PROAIR HFA Inhalation Aerosol, other inhaled drugs and asthma medications should be taken only as directed by your physician. If you are pregnant or nursing, contact your physician about the use of PROAIR HFA Inhalation Aerosol. Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, or nervousness. Effective and safe use of PROAIR HFA Inhalation Aerosol includes an understanding of the way that it should be administered.

Use PROAIR 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").

Drug Interactions

Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with PROAIR 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.

Beta-Blockers: Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as PROAIR 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.

Diuretics: The ECG changes and/or hypokalemia which 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.

Digoxin: Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of 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 albuterol 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 PROAIR HFA Inhalation Aerosol.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: PROAIR 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 cardiovascular system may be potentiated.

Carcinogenesis, Mutagenesis and Impairment of Fertility

In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 15 times the maximum recommended daily inhalation dose for adults 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, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). In a 22-month study in Golden Hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 210 times the maximum recommended daily inhalation dose for adults on a mg/m² basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AHI strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 310 times the maximum recommended daily inhalation dose for adults on a mg/m² basis).

Pregnancy: Teratogenic Effects: Pregnancy Category C

Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m² basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). The drug did not induce cleft palate formation at the low dose (0.025 mg/kg [less than the maximum recommended daily inhalation dose for adults on a mg/m² basis]). Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated subcutaneously with 2.5 mg/kg isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed craniochisis in 7 of 19 (37%) fetuses when albuterol sulfate was administered orally at 50 mg/kg (approximately 630 times the maximum recommended daily inhalation dose for adults on a mg/m² basis).

In an inhalation reproduction study in Sprague-Dawley rats, the albuterol sulfate/HFA-134a formulation did not exhibit any teratogenic effects at 10.5 mg/kg (approximately 65 times the maximum recommended daily inhalation dose for adults on a mg/m² basis).

A study in which pregnant rats were dosed with radiolabeled 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 albuterol sulfate in pregnant women. PROAIR HFA Inhalation Aerosol 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 the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of PROAIR HFA Inhalation Aerosol for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis:

PROAIR HFA Inhalation Aerosol has not been approved for the management of pre-term labor. The benefit/risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with beta-agonists, including albuterol.

Nursing Mothers

Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components of PROAIR HFA Inhalation Aerosol are excreted in human milk. Caution should be exercised when PROAIR HFA Inhalation Aerosol is administered to a nursing woman. Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of PROAIR 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.

Pediatrics

The safety and effectiveness of PROAIR HFA Inhalation Aerosol in pediatric patients below the age of 12 years have not been established.

Geriatrics

Clinical studies of PROAIR HFA Inhalation Aerosol did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually start-

ing at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease 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

A total of 973 subjects were treated with PROAIR HFA Inhalation Aerosol during the worldwide clinical development program.

The adverse reaction information presented in the table below concerning PROAIR HFA Inhalation Aerosol is derived from a 6-week, blinded study which compared PROAIR HFA Inhalation Aerosol (180 mcg four times daily) with a double-blinded matched placebo HFA-Inhalation Aerosol and an evaluator-blinded marketed active comparator HFA-134a albuterol inhaler in 172 asthmatic patients 12 to 76 years of age. The table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the PROAIR HFA Inhalation Aerosol treatment group and more frequently in the PROAIR HFA Inhalation Aerosol treatment group than in the matched placebo group. Overall, the incidence and nature of the adverse events reported for PROAIR HFA Inhalation Aerosol and the marketed active comparator HFA-134a albuterol inhaler were comparable.

Adverse Experience Incidences (% of Patients) in a Six-Week Clinical Trial*				
Body System/Adverse Event (as Preferred Term)	PROAIR HFA Inhalation Aerosol (N = 58)	Marketed active comparator HFA-134a albuterol inhaler (N = 56)	Matched Placebo HFA-134a Inhalation Aerosol (N = 58)	
Body as a Whole	Headache	7	5	2
Cardiovascular	Tachycardia	3	2	0
Musculoskeletal	Pain	3	0	0
Nervous System	Dizziness	3	0	0
Respiratory System	Pharyngitis	14	7	9
	Rhinitis	5	4	2

* This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the PROAIR HFA Inhalation Aerosol group and more frequently in the PROAIR HFA Inhalation Aerosol group than in the placebo HFA Inhalation Aerosol group.

Adverse events reported by less than 3% of the patients receiving PROAIR HFA Inhalation Aerosol but by a greater proportion of PROAIR HFA Inhalation Aerosol patients than the matched placebo patients, which have the potential to be related to PROAIR HFA Inhalation Aerosol, included chest pain, infection, diarrhea, glossitis, accidental injury (nervous system), anxiety, dyspnea, ear disorder, ear pain, and urinary tract infection.

In small cumulative dose studies, tremor, nervousness, and headache were the most frequently occurring adverse events.

Postmarketing

In addition to the adverse events reported in the clinical trials, the following adverse events have been observed in postapproval use of inhaled albuterol. These events have been observed for inclusion due to their seriousness, their frequency of reporting, or their likely beta-mediated mechanism: urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles). Because these events have been reported spontaneously from a population of unknown size, estimates of frequency cannot be made. In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, insomnia, headache, and drying or irritation of the oropharynx.

Post-marketing safety data with PROAIR HFA Inhalation Aerosol are generally consistent with both adverse events in the clinical trials and in the use of inhaled albuterol. Reports have included rare cases of aggravated bronchospasm, lack of efficacy, asthma exacerbation (reported fatal in one case), muscle cramps, and various oropharyngeal side-effects such as throat irritation, altered taste, glossitis, tongue ulceration, and gagging.

OVERDOSAGE

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROAIR HFA Inhalation Aerosol.

Treatment consists of discontinuation of PROAIR HFA Inhalation Aerosol together with appropriate symptomatic therapy. The judicious use of a cardio-selective 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 PROAIR HFA Inhalation Aerosol.

The oral median lethal dose of albuterol sulfate in mice is greater than 2,000 mg/kg (approximately 6,300 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 2,800 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). In young rats, the subcutaneous median lethal dose is approximately 2,000 mg/kg (approximately 13,000 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). The inhalation median lethal dose has not been determined in animals.

Manufactured by:
IVAX Pharmaceuticals Ireland
Waterford, Ireland
For
IVAX Laboratories, Inc.
Miami, FL 33137 USA

Copyright ©2006, IVAX Laboratories, Inc.
All rights reserved.

PROAIR™ is a trademark of IVAX Laboratories, Inc.
Rev. 04/06