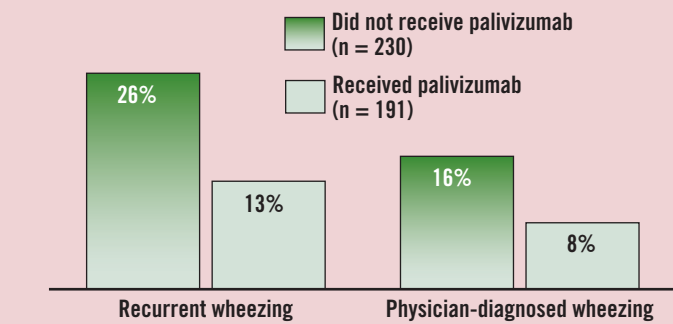


## Wheezing in Preterm Infants Reduced With Palivizumab



Note: Based on a 24-month follow-up.  
Source: Dr. Simoes

# Palivizumab Prophylaxis Cuts Later Wheezing in Premies

BY DIANA MAHONEY  
New England Bureau

**P**alivizumab prophylaxis against respiratory syncytial virus in premature infants without chronic lung disease significantly reduces the incidence and severity of recurrent wheezing, compared with preterm infants not on the preventive therapy, according to a study by Dr. Eric A.F. Simoes of the University of Colorado, Denver, and his colleagues.

Serious RSV infections in the first year of life among preterm infants are associated with an increased risk for developing recurrent wheezing or asthma, as well as persistent abnormal lung function. Because it has been demonstrated in large clinical trials that treatment with palivizumab—a humanized, anti-RSV monoclonal antibody—significantly reduces hospitalization for severe RSV lower respiratory tract infections (LRTI), the authors sought to determine whether preventive treatment with the drug in preterm infants could have an impact on subsequent recurrent wheezing and lung function.

Toward this end, they conducted a prospective investigation of the respiratory outcomes of a retrospectively selected study population of 421 preterm infants, including 191 who had received palivizumab and 230 who did not. None of the infants in the treated group had a prior history of hospitalization for RSV-induced LRTI, while 76 of the untreated group had been hospitalized previously for this condition. Starting at a mean age of 19 months, the children were observed for 24 months for episodes of recurrent wheezing and physician-diagnosed recurrent wheezing. Dr. Simoes and his colleagues reported (*J. Pediatr.* 2007; 151:34-42).

Recurrent wheezing and physician-diagnosed recurrent wheezing were observed in 13% and 8% of the treated infants, respectively, compared with 26% and 16% of the untreated infants. The significant difference remained so after adjusting for potential confounding variables, including baseline RSV-neutralizing antibody titers, family history of asthma, gestational age at birth, birth weight, the number of adults and siblings in the home, and the presence of a wood-burning stove in the home, the authors reported.

Dr. Simoes and his associates also compared the respiratory outcomes of the treated cohort with those of the 154 infants in the untreated cohort who were not previously hospitalized for RSV LRTI; they observed significant relative reductions in both recurrent wheezing and physician-diagnosed recurrent wheezing episodes. This finding suggests that the protective effect of the prophylaxis is related to the drug's efficacy at preventing RSV-induced LRTIs “not just by preventing hospitalization,” they said.

The results of the study are not generalizable to term infants, as the mechanisms leading to recurrent wheezing differ between preterm and term infants. As such, Dr. Simoes and his associates stressed “our findings do not support widespread use of palivizumab.”

In an accompanying editorial, Dr. H. Cody Meissner of Tufts–New England Medical Center in Boston, noted that the findings, if reproducible, “support the theory that avoidance of early RSV infection can reduce the risk of long-term pulmonary complications [in premature infants without chronic lung disease]” (*J. Pediatr.* 2007;151:6-7).

**BRIEF SUMMARY:** Consult the Full Prescribing Information for complete product information.  
**ADDERALL XR<sup>®</sup> CAPSULES**      **Caution: Rx Only**  
AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO LOSS OF EFFICACY. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY. MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

**INDICATIONS:** ADDEPALL XR<sup>®</sup> is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of ADDEPALL XR<sup>®</sup> in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, one controlled trial in adolescents aged 13 to 17, and one controlled trial in adults who met DSM-IV criteria for ADHD, along with extrapolation from the known efficacy of ADDEPALL XR<sup>®</sup>'s immediate-release formulation of this substance.

**CONTRAINDICATIONS:** Advanced atherosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma, agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crisis may result).

**WARNINGS:** Serious Cardiovascular Events: Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems: Children and Adolescents: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems often carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac conditions that may place them at increased risk for the sympathomimetic effects of a stimulant drug (see CONTRAINDICATIONS).

**ADVERSE EVENTS:** Serious Cardiovascular Events: Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems: Children and Adolescents: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems often carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac conditions that may place them at increased risk for the sympathomimetic effects of a stimulant drug (see CONTRAINDICATIONS).

**ADVERSE EVENTS:** Hypertension (See WARNINGS section) In a controlled 4-week outpatient clinical study of adolescents with ADHD, isolated systolic blood pressure elevations  $\geq 20$  mmHg were observed in 704 (11%) placebo-treated patients and 7180 (7%) patients receiving ADDEPALL XR<sup>®</sup> 10 or 20 mg. Isolated elevations in diastolic blood pressure  $\geq 8$  mmHg were observed in 1064 (25%) placebo-treated patients and 22100 (22%) ADDEPALL XR<sup>®</sup>-treated patients. Similar results were observed at higher doses.

**ADVERSE EVENTS:** In a single-dose pharmacokinetic study in 23 adolescents, isolated increases in systolic blood pressure (above the upper 95% CI for age, gender and stature) were observed in 2/17 (12%) and 8/23 (35%) subjects administered 10 mg and 20 mg ADDEPALL XR<sup>®</sup>, respectively. Higher single doses were associated with a greater increase in systolic blood pressure. All increases were transient, appeared maximal at 2 to 4 hours post dose and not associated with symptoms.

**ADVERSE EVENTS:** In a separate placebo-controlled 4-week study in adolescents with ADHD, eight patients (3.4%) discontinued treatment due to adverse events among ADDEPALL XR<sup>®</sup>-treated patients (N=223). Three patients discontinued due to insomnia and one patient each for depression, motor tics, headache, light-headedness, and anxiety.

**ADVERSE EVENTS:** In one placebo-controlled 4-week study among adults with ADHD, patients who discontinued treatment due to adverse events among ADDEPALL XR<sup>®</sup>-treated patients (N=181) were 3.7% (n=6) for nervousness including anxiety and irritability, 2.6% (n=5) for insomnia, 1% (n=2) each for headache, palpitation, and somnolence; and 0.5% (n=1) each for ALT increase, agitation, chest pain, cocaine craving, elevated blood pressure, and weight loss.

**ADVERSE EVENTS:** In a 3-week clinical trial of pediatric patients and a 4-week clinical trial in adolescents and adults, treated with ADDEPALL XR<sup>®</sup> or placebo are presented in the tables below. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, doses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

**ADVERSE EVENTS:** The following adverse reactions have been associated with the use of amphetamines, ADDEPALL XR<sup>®</sup>, or ADDEPALL XR<sup>®</sup> capsules: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiac arrhythmias associated with chronic amphetamine use.

**ADVERSE EVENTS:** Central Nervous System: Psychotic episodes of nonrecommended doses, overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, dysphoria, depression, tremor, headache, exacerbation of motor and phobic tics and Tourette's syndrome, seizures, stroke.

**ADVERSE EVENTS:** Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

**ADVERSE EVENTS:** Allergic: Urticaria, rash, hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported.

**ADVERSE EVENTS:** Endocrine: Impotence, changes in libido.  
**ADVERSE EVENTS:** DRUG ABUSE AND DEPENDENCE: ADDEPALL XR<sup>®</sup> is a Schedule II controlled substance.

**ADVERSE EVENTS:** Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to levels many times higher than recommended. Care and personality changes following prolonged high-dose administration results in extreme fatigue and mental depression; changes are also noted in the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, anorexia, hypertension, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

**ADVERSE EVENTS:** OVERDOSE: Individual patient response to amphetamines varies widely. Toxic symptoms may occur at approximately 1/10 the toxic dose.  
**ADVERSE EVENTS:** Symptoms: Manifestations of acute overdose with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually produced by convulsions and coma.

**ADVERSE EVENTS:** Treatment: Contact with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and/or emesis. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but it is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdose, administration of intravenous phenolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication. The prolonged release of mixed amphetamine salts from ADDEPALL XR<sup>®</sup> should be considered when treating patients with overdose.

**ADVERSE EVENTS:** Dispose in a light, light-resistant container as defined in the USP: Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature].  
**ADVERSE EVENTS:** Manufacturer for: Shire US Inc., Wayne, PA 19087. Made in USA. For more information call 1-800-828-9288, or visit www.adderall.com. ADDEPALL XR<sup>®</sup> and ADDEPALL XR<sup>®</sup> are registered in the US Patent and Trademark Office. Copyright ©2006 Shire US Inc.

**ADVERSE EVENTS:** 003734 381 0137 818  
**ADVERSE EVENTS:** Rev. 6/06 48P518

There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (anal malrotation) in a baby born to a woman who took dextroamphetamine sulfate with levamisole during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nonteratologic Effects:** Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

**Usage in Nursing Mothers:** Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

**Pediatric Use:** ADDEPALL XR<sup>®</sup> is indicated for use in children 6 years of age and older.

**Use in Children Under Six Years of Age:** Effects of ADDEPALL XR<sup>®</sup> in 3-5 year olds have not been studied. Long-term effects of amphetamines in children have not been established. Amphetamines are not recommended for use in children under 2 years of age.

**Geriatric Use:** ADDEPALL XR<sup>®</sup> has not been studied in the geriatric population.

**ADVERSE EVENTS:** Hypertension (See WARNINGS section) In a controlled 4-week outpatient clinical study of adolescents with ADHD, isolated systolic blood pressure elevations  $\geq 20$  mmHg were observed in 704 (11%) placebo-treated patients and 7180 (7%) patients receiving ADDEPALL XR<sup>®</sup> 10 or 20 mg. Isolated elevations in diastolic blood pressure  $\geq 8$  mmHg were observed in 1064 (25%) placebo-treated patients and 22100 (22%) ADDEPALL XR<sup>®</sup>-treated patients. Similar results were observed at higher doses.

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**ADVERSE EVENTS:** The premarketing development program for ADDEPALL XR<sup>®</sup> included exposures in a total of 1215 participants in clinical trials (856 pediatric patients, 358 adolescent patients, 242 adult patients, 62 healthy adult subjects). Of these, 635 patients (ages 6 to 12) were included in two controlled clinical studies, one open-label clinical study, and two single-dose clinical pharmacology studies (N=42). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, electrocardiograms, and ECGs.

**ADVERSE EVENTS:** Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to clearly report adverse events.

**ADVERSE EVENTS:** The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.

**ADVERSE EVENTS:** Adverse events associated with discontinuation of treatment: In two placebo-controlled studies of up to 5 weeks duration among children with ADHD, 2.4% (10/425) of ADDEPALL XR<sup>®</sup>-treated patients discontinued due to adverse events (including 3 patients with loss of appetite, one of whom also reported insomnia) compared to 2.1% (2/928) receiving placebo. The most frequent adverse events associated with discontinuation of ADDEPALL XR<sup>®</sup> in children and adolescents, multiple-dose clinical trials of pediatric patients (N=585) are presented below. Over half of these patients were exposed to ADDEPALL XR<sup>®</sup> for 12 weeks or more.

Adverse event	% of pediatric patients discontinued treatment
Anorexia (loss of appetite) (reported)	2.6
Weight loss	1.3
Emotional lability	1.0
Depression	0.7

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**ADVERSE EVENTS:** Adverse events occurring in a controlled trial: Adverse events reported in a 3-week clinical trial of pediatric patients and a 4-week clinical trial in adolescents and adults, treated with ADDEPALL XR<sup>®</sup> or placebo are presented in the tables below. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, doses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

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**ADVERSE EVENTS:** Manufacturer for: Shire US Inc., Wayne, PA 19087. Made in USA. For more information call 1-800-828-9288, or visit www.adderall.com. ADDEPALL XR<sup>®</sup> and ADDEPALL XR<sup>®</sup> are registered in the US Patent and Trademark Office. Copyright ©2006 Shire US Inc.

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