

## VERBATIM

“My son and I have a close relationship. ... I do take him on rounds with me occasionally when I’m covering call on the weekend. He enjoys going to the hospital and it helps that I’m in pediatrics. I can come into a room with a child patient and it’s very reassuring to these young kids to see that I have a “child assistant.””

Boston pediatric rheumatologist Dr. John Whelan on his life as a divorced dad, p. 62

# Studies Uncover Adverse Reactions to Probiotics

BY ROBERT FINN  
San Francisco Bureau

BEVERLY HILLS, CALIF. — The jury may still be out on whether probiotics are beneficial, but at least they do no harm and can be safely recommended to patients, right? Not so, said Dr. David R. Mack at the International Probiotics As-

sociation World Congress. Several recent studies have uncovered some risks associated with probiotic use, in both children and adults. “We [physicians] are always looking for new things, but we’re a conservative, skeptical lot, and safety is a primary concern.”

One of the most concerning studies is also one of the newest, noted Dr. Mack of the University of Ottawa (Ont.). Investigators randomized 298 patients with predicted acute pancreatitis to receive probiotic prophylaxis or placebo. The probiotic preparation consisted of six live bacterial species: *Lactobacillus acidophilus*, *L. casei*, *L. salivarius*,

*Lactococcus lactis*, *Bifidobacterium bifidum*, and *B. lactis*.

**In one study, the mortality rate was 2.5 times higher among the patients receiving probiotics than among those receiving placebo.**

Not only did the probiotic preparation fail to reduce the risk of infectious complications, but the mortality rate was 2.5 times higher among the patients receiving probiotics than among those receiving placebo.

Twenty-four (16%) of the patients in the probiotics group died, compared with nine (6%) in the placebo group.

Furthermore, nine of the patients in the probiotics group developed bowel ischemia (eight with fatal outcomes), compared with none in the placebo group. The other deaths involved multiorgan failure (Lancet 2008;371:651-9).

According to some studies, probiotics are associated with increased asthma and wheezing in children. In one study, for example, children exposed to *L. rhamnosus* GG at birth had 3.4 times the risk of having asthma at age 7 years as a control group had (J. Allergy Clin. Immunol. 2007;119:1019-21). In another study involving the use of *L. rhamnosus* GG to prevent atopic dermatitis, 26% of the children in the probiotic group versus 9% in the control group developed wheezing bronchitis (Pediatrics 2008;121:e850-6 [Epub doi:10.1542/peds.2007-1492]).

And there is further evidence of possible allergic complications following probiotic use. One study in France demonstrated that two out of three common probiotic preparations contained cow’s milk proteins (J. Allergy Clin. Immunol. 2007;119:746-7), and a separate case report described a child who developed anaphylaxis after taking a probiotic containing cow’s milk proteins (Allergy 2006;61:507-8). Beyond these known adverse reactions, there are other reasons to be concerned about the possible long-term effects of probiotics in young children. When adults take probiotics, it’s rare to see extended colonization by the probiotic bacterial species, but outcomes appear to be different in young children: Some probiotic species have been detected in stool samples years later. ■

## XYZAL®

(levocetirizine dihydrochloride)

5 mg tablets

Rx only

Brief Summary of Prescribing Information

**INDICATIONS AND USAGE: Allergic Rhinitis:** XYZAL® is indicated for the relief of symptoms associated with allergic rhinitis (seasonal and perennial) in adults and children 6 years of age and older.

**Chronic Idiopathic Urticaria:** XYZAL is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older.

**DOSAGE AND ADMINISTRATION:** XYZAL is available as 2.5 mg/5 mL (0.5 mg/mL) oral solution and as 5 mg breakable (scored) tablets, allowing for the administration of 2.5 mg, if needed. XYZAL can be taken without regard to food consumption.

**Adults and Children 12 Years of Age and Older:** The recommended dose of XYZAL is 5 mg (1 tablet or 2 teaspoons [10 mL] oral solution) once daily in the evening. Some patients may be adequately controlled by 2.5 mg (1/2 tablet or 1 teaspoon [5 mL] oral solution) once daily in the evening.

**Children 6 to 11 Years of Age:** The recommended dose of XYZAL is 2.5 mg (1/2 tablet or 1 teaspoon [5 mL] oral solution) once daily in the evening. The 2.5 mg dose should not be exceeded because the systemic exposure with 5 mg is approximately twice that of adults (see *Clinical Pharmacology* in Full Prescribing Information).

XYZAL is not indicated for children under 6 years of age.

**Dose Adjustment for Renal and Hepatic Impairment:** In patients ≥12 years of age with: Mild renal impairment ( $Cl_{CR}$  = 50-80 mL/min) - 2.5 mg once daily is recommended; moderate renal impairment ( $Cl_{CR}$  = 30-50 mL/min) - 2.5 mg once every other day; severe renal impairment ( $Cl_{CR}$  = 10-30 mL/min) - 2.5 mg twice weekly (once every 3-4 days). Patients with end-stage renal disease ( $Cl_{CR}$  < 10 mL/min) and patients undergoing hemodialysis should not receive XYZAL.

No dose adjustment is needed in patients with solely hepatic impairment. In patients with both hepatic and renal impairment, adjustment of the dose is recommended.

### CONTRAINDICATIONS

The use of XYZAL is contraindicated in:

- Patients with known hypersensitivity to levocetirizine or any of the ingredients of XYZAL, or to cetirizine. Observed reactions range from urticaria to anaphylaxis (see *ADVERSE REACTIONS, Post-Marketing Experience*).
- Patients with end-stage renal disease ( $Cl_{CR}$  < 10 mL/min) and patients undergoing hemodialysis.
- Pediatric patients 6 to 11 years of age with impaired renal function (see *USE IN SPECIFIC POPULATIONS, Pediatric Use*).

**WARNINGS AND PRECAUTIONS: Activities Requiring Mental Alertness:** In clinical trials the occurrence of somnolence, fatigue, and asthenia has been reported in some patients under therapy with XYZAL. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, and motor coordination such as operating machinery or driving a motor vehicle after ingestion of XYZAL. Concurrent use of XYZAL with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur.

**ADVERSE REACTIONS:** Use of XYZAL has been associated with somnolence, fatigue, and asthenia (see *WARNINGS AND PRECAUTIONS, Activities Requiring Mental Alertness*).

**Clinical Trials Experience:** The safety data described below reflect exposure to XYZAL in 2549 patients with seasonal or perennial allergic rhinitis and chronic idiopathic urticaria in 12 controlled clinical trials of 1 week to 6 months duration. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice.

**Adults and Adolescents 12 years of Age and Older:** In studies up to 6 weeks in duration, the mean age of the adult and adolescent patients was 32 years, 44% of the patients were men and 56% were women, and the large majority (more than 90%) was Caucasian.

In these trials 43% and 42% of the subjects in the XYZAL 2.5 mg and 5 mg groups, respectively, had at least one adverse event compared to 43% in the placebo group.

In placebo-controlled trials of 1-6 weeks in duration, the most common adverse reactions were somnolence, nasopharyngitis, fatigue, dry mouth, and pharyngitis, and most were mild to moderate in intensity. Somnolence with XYZAL showed dose ordering between tested doses of 2.5, 5 and 10 mg and was the most common adverse reaction leading to discontinuation (0.5%).

In clinical trials, the most common adverse reactions in ≥ 2% of adult and adolescent patients (12 years of age and older) taking XYZAL 2.5 mg, XYZAL 5 mg, or placebo were somnolence (5%, 6%, 2%), nasopharyngitis (6%, 4%, 3%), fatigue (1%, 4%, 2%), dry mouth (3%, 2%, 1%), and pharyngitis (2%, 1%, 1%), respectively.

Additional adverse reactions of medical significance observed at a higher incidence than in placebo in adults and adolescents aged 12 years and older exposed to XYZAL are syncope (0.2%) and weight increased (0.5%).

**Pediatric Patients 6 to 12 Years of Age:** A total of 243 pediatric patients 6 to 12 years of age received XYZAL 5 mg once daily in two short-term placebo controlled double-blind trials. The mean age of the patients was 9.8 years, 79 (32%) were between 6-8 years of age, and 50% were Caucasian.

The safety of XYZAL in children under 6 years of age has not been established [see *Use in Specific Populations* (8.4)].

In clinical trials, the most common adverse reactions in ≥ 2% of pediatric patients (6 to 12 years of age) taking XYZAL 5 mg or placebo, and were more common with XYZAL than placebo were pyrexia (4%, 2%), cough (3%, <1%), somnolence (3%, <1%), epistaxis (2%, <1%), respectively.

**Long-Term Clinical Trials Experience:** In two controlled clinical trials, 428 patients (190 males and 238 females) aged 12 years and older were treated with XYZAL 5 mg once daily for 4 or 6 months. The patient characteristics and the safety profile were similar to that seen in the short-term studies. Ten (2.3%) patients treated with XYZAL discontinued because of somnolence, fatigue or asthenia compared to 2 (<1%) in the placebo group.

**Laboratory Test Abnormalities:** Elevations of blood bilirubin and transaminases were reported in <1% of patients in the clinical trials. The elevations were transient and did not lead to discontinuation in any patient.

**Post-Marketing Experience:** In addition to the adverse reactions reported during clinical trials and listed

above, adverse events have also been identified during post-approval use of XYZAL in other countries. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Adverse events of hypersensitivity and anaphylaxis, angioneurotic edema, fixed drug eruption, pruritus, rash, and urticaria, convulsion, aggression and agitation, visual disturbances, palpitations, dyspnea, nausea, hepatitis, and myalgia have been reported.

Besides these events reported under treatment with XYZAL, other potentially severe adverse events have been reported from the post-marketing experience with cetirizine. Since levocetirizine is the principal pharmacologically active component of cetirizine, one should take into account the fact that the following adverse events could also potentially occur under treatment with XYZAL: hallucinations, suicidal ideation, orofacial dyskinesia, severe hypotension, cholestasis, glomerulonephritis, and still birth.

**DRUG INTERACTIONS:** *In vitro* data indicate that levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drug-metabolizing enzymes. No *in vivo* drug-drug interaction studies have been performed with levocetirizine. Drug interaction studies have been performed with racemic cetirizine.

**Antipyrine, Azithromycin, Cimetidine, Erythromycin, Ketoconazole, Theophylline, and Pseudoephedrine:** Pharmacokinetic interaction studies performed with racemic cetirizine demonstrated that cetirizine did not interact with antipyrine, pseudoephedrine, erythromycin, azithromycin, ketoconazole, and cimetidine. There was a small decrease (~16%) in the clearance of cetirizine caused by a 400 mg dose of theophylline. It is possible that higher theophylline doses could have a greater effect.

**Ritonavir:** Ritonavir increased the plasma AUC of cetirizine by about 42% accompanied by an increase in half-life (53%) and a decrease in clearance (29%) of cetirizine. The disposition of ritonavir was not altered by concomitant cetirizine administration.

**USE IN SPECIFIC POPULATIONS: Pregnancy:** Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, XYZAL should be used during pregnancy only if clearly needed.

**Nursing Mothers:** No peri- and post-natal animal studies have been conducted with levocetirizine. Cetirizine has been reported to be excreted in human breast milk. Because levocetirizine is also expected to be excreted in human milk, use of XYZAL in nursing mothers is not recommended.

**Pediatric Use:** The safety and effectiveness of XYZAL in pediatric patients under 6 years of age have not been established.

The recommended dose of XYZAL for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in patients 12 to 17 years of age is based on extrapolation of efficacy from adults 18 years of age and older (see *CLINICAL STUDIES* in Full Prescribing Information).

The recommended dose of XYZAL in patients 6 to 11 years of age for the treatment of the symptoms of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria is based on cross-study comparison of the systemic exposure of XYZAL in adults and pediatric patients and on the safety profile of XYZAL in both adult and pediatric patients at doses equal to or higher than the recommended dose for patients 6 to 11 years of age.

The safety of XYZAL 5 mg once daily was evaluated in 243 pediatric patients 6 to 12 years of age in two placebo-controlled clinical trials lasting 4 and 6 weeks (see *ADVERSE REACTIONS, Clinical Trials Experience*). The effectiveness of XYZAL 2.5 mg once daily for the treatment of the symptoms of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria in children 6 to 11 years of age is supported by the extrapolation of demonstrated efficacy of XYZAL 5 mg once daily in patients 12 years of age and older and by the pharmacokinetic comparison in adults and children.

Cross-study comparisons indicate that administration of a 5 mg dose of XYZAL to 6-12 year old pediatric seasonal allergic rhinitis patients resulted in about 2-fold the systemic exposure (AUC) observed when 5 mg of XYZAL was administered to healthy adults. Therefore, in children 6 to 11 years of age the recommended dose of 2.5 mg once daily should not be exceeded (see *DOSAGE AND ADMINISTRATION, Children 6 to 11 Years of Age; CLINICAL STUDIES* in Full Prescribing Information and *CLINICAL PHARMACOLOGY, Pharmacokinetics* in Full Prescribing Information).

**Geriatric Use:** Clinical studies of XYZAL for each approved indication did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than 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 disease or other drug therapy.

**Renal Impairment:** XYZAL is known to be substantially excreted by the kidneys and the risk of adverse reactions to this drug 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 (see *DOSAGE AND ADMINISTRATION* and *Clinical Pharmacology, Pharmacokinetics* in Full Prescribing Information).

**Hepatic Impairment:** As levocetirizine is mainly excreted unchanged by the kidneys, it is unlikely that the clearance of levocetirizine is significantly decreased in patients with solely hepatic impairment (see *CLINICAL PHARMACOLOGY, Pharmacokinetics* in Full Prescribing Information).

**OVERDOSAGE:** Overdosage has been reported with XYZAL.

Symptoms of overdose may include drowsiness in adults and initially agitation and restlessness, followed by drowsiness in children. There is no known specific antidote to XYZAL. Should overdose occur, symptomatic or supportive treatment is recommended. XYZAL is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested.

The acute maximal non-lethal oral dose of levocetirizine was 240 mg/kg in mice (approximately 200 times the maximum recommended daily oral dose in adults and approximately 230 times the maximum recommended daily oral dose in children) on a mg/m<sup>2</sup> basis. In rats the maximal non-lethal oral dose was 240 mg/kg (approximately 390 times the maximum recommended daily oral dose in adults and approximately 460 times the maximum recommended daily oral dose in children on a mg/m<sup>2</sup> basis).



sanofi aventis

Manufactured for: UCB, Inc. • Smyrna, GA 30080  
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