

'Ugly Duckling' Melanoma Screen Is Easy, Effective

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WAIKOLOA, HAWAII — The "ugly duckling" sign showed impressive sensitivity for melanoma when applied by physicians as well as nonmedically trained individuals for rating melanocytic lesions, according to Dr. Ashfaq A. Marghoob.

The results of this study suggest the ugly duckling sign may be a valuable melanoma screening tool readily teachable

to primary care physicians, nurse practitioners, and patients performing periodic skin self-examination, Dr. Marghoob reported at the annual Hawaii dermatology seminar sponsored by Skin Disease Education Foundation.

"Could this be a new public health message?" he asked. "For the last 20 or 30 years we've been talking about the ABCD features, but maybe we could add something along the lines of, 'Look for the ABCD features, but if you see a lesion on your skin

that looks different than the surrounding lesions on your skin—even if it doesn't have the ABCDs—see a dermatologist.'"

The ugly duckling sign was first described in 1998 by Dr. Jean-Jacques Grob of the University of Marseille in Provence, France. It holds that nevi on a given individual tend to resemble each other: "Moles breed true," said Dr. Marghoob, a dermatologist at Memorial Sloan-Kettering Cancer Center, New York.

The ugly duckling—the outlier, the ex-

ceptional nevus, the one that looks different from the others—is more likely to be a melanoma, even if it does not exhibit the classic features ascribed to melanoma in the ABCD rule.

The ABCD acronym "has served us well" in the early recognition of melanoma, said Dr. Marghoob, but it has shortcomings: There is morphologic overlap with dysplastic nevi, resulting in many unnecessary excisions. Also, the ABCD criterion does not fit for many thin melanomas.

To test the utility of the ugly duckling sign when applied by a diverse group of people, Dr. Marghoob and coinvestigators assembled a portfolio of digital photographs of the backs of 12 patients at high risk for melanoma. Each of the patients had at least eight dysplastic nevi on their back.



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DR. MARGHOOB

In five patients, one of the skin lesions was a melanoma which was removed and histologically confirmed after the pictures were taken. The photo spread included whole-back overview images as well as clinical closeups of a total of 145 lesions.

The lesion raters consisted of 13 general dermatologists, 8 dermatologists with special expertise in pigmented lesions, 5 nurses, and 8 secretaries and other non-clinical hospital staff. They were asked if any of the 145 nevi differed from the others on the patients' backs.

There was excellent agreement on the ugly duckling sign among observers. All five melanomas but only 3 of 140 benign nevi were identified as ugly duckling lesions by at least two-thirds of the raters. The sensitivity of the ugly duckling sign—that is, the percentage of melanomas identified as "different"—was 100% for the experts, 89% for the general dermatologists, 88% for the nurses, and 85% for the nonclinicians. For the overall group, the sensitivity of the ugly duckling sign was 90% (Arch. Dermatol. 2008;144:58-64).

That 85% sensitivity when the ugly duckling sign was applied by nonclinicians is much higher than the percentage seen in studies of the ABCD method, Dr. Marghoob observed.

He noted that the overall melanoma survival rate in the United States has soared from less than 60% in 1970 to greater than 90% in 2008. This extremely impressive gain is mainly a result of improved detection of early disease, since there are still no effective systemic therapies for advanced melanoma.

Widespread adoption of the ugly duckling sign could be a further step forward in early diagnosis of melanoma. Total body photography, dermoscopy, and confocal microscopy are additional tools likely to lead to further improvements, he said.

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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.

DOSE AND ADMINISTRATION

XYZAL is available 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 once daily in the evening. Some patients may be adequately controlled by 2.5 mg once daily in the evening.

Children 6 to 11 Years of Age – The recommended dose of XYZAL is 2.5 mg (1/2 tablet) 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, Pharmacokinetics in Full Prescribing Information).

Dose Adjustment for Renal and Hepatic Impairment – In adults and children 12 years of age and older with:

- Mild renal impairment (creatinine clearance [CL_{CR}] = 50-80 mL/min): a dose of 2.5 mg once daily is recommended;
- Moderate renal impairment (CL_{CR} = 30-50 mL/min): a dose of 2.5 mg once every other day is recommended;
- Severe renal impairment (CL_{CR} = 10-30 mL/min): a dose of 2.5 mg twice weekly (administered once every 3-4 days) is recommended;
- End-stage renal disease patients (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 impairment 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. The short-term (exposure up to 6 weeks) safety data for adults and adolescents are based upon eight clinical trials in which 1896 patients (825 males and 1071 females aged 12 years and older) were treated with XYZAL 2.5, 5, or 10 mg once daily in the evening. The short-term safety data from pediatric patients are based upon two clinical trials in which 243 children with seasonal or perennial allergic rhinitis (162 males and 81 females 6 to 12 years of age) were treated with XYZAL 5 mg once daily for 4 to 6 weeks. The long-term (exposure of 4 or 6 months) safety data are based upon two clinical trials in adults and adolescents in which 428 patients (190 males and 238 females) with allergic rhinitis were exposed to treatment with XYZAL 5 mg once daily. 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%).

Table 1 lists adverse reactions that were reported in greater than or equal to 2% of subjects aged 12 years and older exposed to XYZAL 2.5 mg or 5 mg in eight placebo-controlled clinical trials and that were more common with XYZAL than placebo.

Table 1 Adverse Reactions Reported in ≥ 2%* of Subjects Aged 12 Years and Older Exposed to XYZAL 2.5 mg or 5 mg in Placebo-Controlled Clinical Trials 1-6 Weeks in Duration

Adverse Reactions	XYZAL 2.5 mg (n = 421)	XYZAL 5 mg (n = 1070)	Placebo (n = 912)
Somnolence	22 (5%)	61 (6%)	16 (2%)
Nasopharyngitis	25 (6%)	40 (4%)	28 (3%)
Fatigue	5 (1%)	46 (4%)	20 (2%)
Dry Mouth	12 (3%)	26 (2%)	11 (1%)
Pharyngitis	10 (2%)	12 (1%)	9 (1%)

*Rounded to the closest unit percentage

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. Table 2 lists adverse reactions that were reported in greater than or equal to 2% of subjects aged 6-12 years exposed to XYZAL 5 mg in placebo-controlled clinical trials and that were more common with XYZAL than placebo.

Table 2 Adverse Reactions in Subjects Aged 6-12 Years Reported in ≥ 2%* for XYZAL 5 mg in Placebo-Controlled Clinical Trials 4 and 6 Weeks in Duration

Adverse Reactions	XYZAL 5 mg/day (n = 243)	Placebo (n = 240)
Pyrexia	10 (4%)	5 (2%)
Cough	8 (3%)	2 (<1%)
Somnolence	7 (3%)	1 (<1%)
Epistaxis	6 (2%)	1 (<1%)

*Rounded to the closest unit percentage

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, angioedema, 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

In rats and rabbits, levocetirizine was not teratogenic at oral doses up to 200 and 120 mg/kg, respectively (approximately 320 and 390 times the maximum recommended daily oral dose in adults on a mg/m² basis). There are, however, 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. In mice, cetirizine caused retarded pup weight gain during lactation at an oral dose in dams of 96 mg/kg (approximately 40 times the maximum recommended daily oral dose in adults on a mg/m² basis). Studies in beagle dogs indicated that approximately 3% of the dose of cetirizine was excreted in milk. 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. 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 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/m² 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/m² basis).



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