# Panel Rejects Omalizumab for 6- to 11-Year-Olds

BY ELIZABETH MECHCATIE

SILVER SPRING, MD. — The majority of a Food and Drug Administration advisory panel did not support expanding the approval of omalizumab as a treatment for moderate to severe persistent asthma to include children aged 6-11 years, based on available safety and efficacy data.

The FDA's Pulmonary-Allergy Drugs

Advisory Committee voted 10-4 that the safety and efficacy data on omalizumab did not provide "substantial and convincing evidence" to support approval for the proposed indication: the treatment of asthma in patients aged 6-11 years with moderate to severe persistent asthma whose symptoms are inadequately controlled with inhaled corticosteroids (ICS) and who have a positive skin test or in vitro reactivity to

a perennial aeroallergen. Omalizumab, a monoclonal antibody that reduces serum IgE levels, was approved in 2003 for the same indication in adolescents and adults aged 12 years and older.

It is marketed as Xolair by Genentech USA Inc. and Novartis Pharmaceuticals.

A marginal effect on efficacy and outstanding safety issues, including concerns about long-term safety, anaphylaxis risk, and unknown implications of circulating levels of omalizumab-IgE immune complexes in some treated patients, were among the reasons panelists said they voted against approval.

Omalizumab is administered subcutaneously, every 2-4 weeks in a health care setting, at a dose based on serum IgE levels and body weight. The current label includes warnings about the potential risks of anaphylaxis and malignancies associated with treatment, based on data in clinical trials and postmarketing reports. In July 2009, the FDA reported that a cardiovascular safety signal associated with omalizumab was identified in post-marketing re-

Omalizumab was evaluated in a pivotal 52-week study of 627 children aged 6-11 years with moderate to severe persistent, inadequately controlled allergic asthma, despite treatment with fluticas-

Panelists had concerns about the agent's long-term safety, anaphylaxis risk, and unknown implications of circulating omalizumab-lgE immune complexes in some patients.

one at a dose of 200 mcg or more per day (or the equivalent), with or without other controller medications, which included short-acting beta-agonists (a mean of 2.8 puffs/day) and leukotriene antagonists (37%).

The primary end point, the rate of clinically significant asthma exacerbations (defined as worsening of symptoms requiring a doubling of the baseline ICS dose for 3 days or more and/or treatment with rescue systemic intravenous or oral steroids for 3 days) at 24 weeks, was 0.45 among those treated with omalizumab, compared with 0.64 among those on placebo, which was statistically significant.

One secondary efficacy end point, the asthma exacerbation rate at 52 weeks, was significant in favor of omalizumab (0.78 among those on omalizumab, compared with 1.30 among those on placebo).

The other secondary end points—nocturnal symptom scores, asthma medication rescue use, and quality of life scores at 24 weeks—were not significantly different between the two groups. The most common adverse effects in pediatric studies were nasopharyngitis, upper respiratory tract infections, and headache; these were reported at similar rates in those on placebo and omalizumab.

No new safety signals were identified, and there were no malignancies among omalizumab-treated patients. The one case of anaphylaxis in an omalizumabtreated patient was associated with a meperidine hydrochloride (Demerol) injection.

The FDA usually follows the recommendations of its advisory panels.

Table 3 Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body System - Preferred term	75 mg/d [N=84] %	150 mg/d [N=302] %	300 mg/d [N=312] %	600 mg/d [N=154] %	All PGB* [N=852] %	Placebo [N=398] %
Body as a whole						
Infection	14	8	6	3	7	4
Headache	5	9	5	8	7	5
Pain	5	4	5	5	5	4
Accidental injury	4	4 3 2 2	5 3 2	5	5 3 2 2	2
Flu syndrome	1	2	2	1	2	1
Face edema	0	2	1	3	2	1
Digestive system	-	-		-	-	
Dry mouth	7	7	6	15	8	3
Constipation	Δ	5		5		2
Flatulence	ż	ĭ	5 2	3	2	ī
Vomiting	ī	1	3	3	5 2 2	1
Metabolic and nutrition	al disorders		-	-	-	
Peripheral edema	0	8	16	16	12	4
Weight gain	ĭ	2	5	7	4	Ó
Edema	ń	1	2	6	2	1
Musculoskeletal syste	m		-		-	
Myasthenia	1	1	1	1	1	0
Nervous system						-
Dizziness	11	18	31	37	26	9
Somnolence	8	12	18	25	16	5
Ataxia	1		5	9	5	1
Abnormal gait	ń	2 2 2 2 2	ă.	8		i
Confusion	ĭ	2	3	7	4 3 2 2 2	Ó
Thinking abnormal <sup>1</sup>	Ó	2	1	6	2	2
Incoordination	2	2	i	3	2	ō
Amnesia	ñ	ī	i	ă.	2	ŏ
Speech disorder	n	'n	1	3	1	ñ
Respiratory system	· ·	0				
Bronchitis	Π	1	1	3	1	1
Special senses						
Blurry vision <sup>‡</sup>	1	5	5	9	5	3
Diplopia	ń	2	2	ă.	2	ň
Ahnormal vision	0	1	2	5	2	ů.
Eve disorder	0	1	1	2	1	0
Urogenital system	U	'	'	2	'	U
Urinary incontinence	0	1	1	2	1	0

PGB: pregabatin
Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language
problems and slowed thinking.
Investigator term; summany level term is amblyopia.

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The consequence of the control of the Clinical Studies of LYRICA Following is a list of treatment-emergent adverse reactions reported by patients treated with LYRICA during all clinical trials. The listing does not include those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse reactions are those occurring in 1700 to 17/100 patients; racreactions are those occurring in fewer than 17/100 patients. Events of major clinical importance are described in the Warnings and Precautions section. Body as a Whole – Frequent: Abdominal pain, Allergic reaction, Fever, Infrequent: Abosecs, Cellulitis, Chills, Malais, Ker rigidity, Overdose, Pelvic pain, Photosensitivity reaction; Rare: Anaphylactoid reaction, Ascites, Granuloma, Hangover effect, Intentional Injury, Retropertionael Thirorsis, Shock, Cardiovascular System – Infrequent: Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope, Infrequent Cholecytitis, Cholelithiasis, Colitis, System – Frequent: Echymosis, Infrequent Abordomina, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; Rare: Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Lymphadenopathy, Thrombocytopenia; Rare: Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Lympotina, Myelogenia, Dysathria, Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Myelofibrosis, Polycythem

# DRUG INTERACTIONS

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Since LYRICA is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. In vitro and in vivo studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topicamete. Important pharmacokinetic interactions would also not be expected to occur between LYRICA and commonly used antiepileptic drugs. Pharmacodynamics Multiple oral doses of LYRICA were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on congritive and gross motor functioning were seen when LYRICA was co-administered with these drugs. No clinically important effects on respiration were seen.

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USE IN SPECIFIC POPULATIONS
Pregnancy Pregnancy Category C. Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) ≥5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at ≥1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The vode sois in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for for rat embryo-fetal developmental toxicity was not established. When pregnant rabbits were given LYRICA (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD. In a study in which female rats were dosed with LYRICA (50, 100, 250, 1250, or 2500 mg/kg) throughout ty estation and lactation, offspring growth was reduced at ≥100 mg/kg and offspring survival was pronouced at doses ≥11250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased act auditory startle responding) were observed at ≥25

toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD. There are no adequate and well-controlled studies in pregnant women. LYRICA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To provide information regarding the effects of in utero exposure to LYRICA, physicians are advised to recommend that pregnant patients taking LYRICA enroll in the North American Antiepileptic Drug (INAEEI) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/. Labor and Delivery The effects of LYRICA on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥50 times the mean human exposure (AUC <sub>0-24)</sub> of 123 µg-hr/mL) at the maximum recommended clinical dose of 600 mg/dey. **Nursing Mothers** It is not known if pregabalin is excreted in human milk; at is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, 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. Pediatric Use The safety and efficacy of prepabalin in pediatric patients have not been established. In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral chaphenavioral chaphenavioral chaphenavioral chaphenavioral chaphenavioral chaphenavioral chaphenavioral chappes of acoustic startle persisted at ≥500 mg/kg and administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral chappes of acoustic startle persisted at ≥

# DRUG ABUSE AND DEPENDENCE

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Controlled Substance LYRICA is a Schedule V controlled substance. LYRICA is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior). Abuse In a study of recreational users (N=15) of sedative/hymotic drugs, including alcohol, LYRICA (450 mg, single dose). Len controlled clinical studies in over 5500 patients, 4% of LYRICA-treated patients and 1% of placebo-treat patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. Dependence In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache or diarrhea [see Warnings and Precautions], suggestive of

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans There is limited experience with overdose of LYRICA. The highest reported accidental overdose of LYRICA during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse reactions experienced by patients exposed to higher doses (≥900 mg) were not clinically different from those of patients administered recommended doses of LYRICA. Treatment or Management of Overdoss There is no specific antidate for overdose with LYRICA. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with LYRICA. Although hemodialysis has not been performed in the few known cases of overdose, if may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

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NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis A dose-dependent increase in the incidence carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis A dose-dependent increase in the incidence carcinogenesis and control of the control (MRD) (An Extra Caroline) in the fours).

Noncinklea Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (BBC3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD. Mutagenesis Pregabalin was not mutagenic in bacteria or in mammalian cells in vitro, was not clastogenic in mammalian systems in vitro and in vivo, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes. Impairment of Fertility In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motifity, increased sperm abnormalities, reduced fertility, increased sperm administration embryo loss, decreased intensive studies (100 mg/kg) was associated with a plasma prepabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. In addition, adverse reactions on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive

adequately studied. 
Animal Toxicology and/or Pharmacology Dermatopathy Skin lesions ranging from erythema to necrosis were seen in repeated-dose boxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions wo observed in clinical studies. <a href="December 40">December 40</a> in Clember 40">December 40</a> in Clember 40">December 40">December



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