

# FDA Delays Changes to Concerta Label Until 2006

BY DEBORAH LEVENSON

Contributing Writer

ROCKVILLE, MD. — A Food and Drug Administration panel has decided to postpone changes to safety warnings in the label for Concerta, a stimulant widely prescribed for attention-deficit hyperactivity disorder.

The FDA's Pediatric Advisory Committee recommended that agency officials delay any possible changes until data on ad-

verse events associated with all methylphenidates (including Ritalin, Methylin, and Metadate) have been analyzed. Some committee members said they were unsure whether certain events were caused by the drugs or by underlying conditions. That review probably won't be complete until early 2006, according to Anne Trontell, M.D., deputy director of the FDA's Office of Drug Safety.

The FDA's legally required 1-year post-exclusivity data review for Concerta ex-

amined reports of adverse psychiatric and cardiovascular events, including hallucinations, suicidal ideation, psychotic behavior, hypertension, and arrhythmias.

Although FDA officials and members of the Pediatric Advisory Committee agreed that these reports don't give new or unusual information, most also noted that existing warnings about possible adverse events could be better presented on the Concerta label, which now includes information in seven different places.

The FDA wants to update safety information on the labels on Concerta and other methylphenidates because prescribing practices have changed drastically since the first such drug (Ritalin) entered the market in 1955, said Paul J. Andreason, M.D., of the FDA's division of neuropharmacological drug products.

Calling methylphenidates "remarkably effective," Richard Gorman, M.D., representative for the American Academy of Pediatrics, noted the public perception that methylphenidates are dangerous.

"Nothing I've heard today about these medications makes me particularly concerned," said pediatric epidemiologist Thomas B. Newman, M.D., of the University of California, San Francisco.

Most committee members also urged FDA officials to let physicians and the public know why the FDA is postponing changes to safety information on the Concerta label and that the FDA is continuing to monitor methylphenidate problems.

Michael E. Fant, M.D., a neonatologist and biochemist at the University of Texas, Houston, also suggested studying the drug's effects on younger children.

Dianne Murphy, M.D., director of the FDA's Office of Pediatric Therapeutics, added that exclusivity trials showed differences in metabolism and clearance among 3- to 8-year-olds, and added that exclusivity studies did not involve younger children.

FDA committee members also considered information from a small study of Ritalin that suggests it is associated with chromosome aberrations in peripheral blood lymphocytes, an independent risk factor for cancer.

That study by Randa A. El-Zein, M.D., and colleagues, published earlier this year in *Cancer Letters*, was the topic of an on-site evaluation by officials at the FDA and other federal agencies. They determined the study had methodology flaws, including a lack of placebo controls and unusual data presentation, said David Jacobson-Kram, Ph.D., of the FDA's Office of New Drugs.

He added that researchers don't know how the drug can damage DNA.

The Texas researchers are seeking funding to perform a larger study, while the FDA, the National Institute of Child Health and Human Development, the National Institute of Environmental Health Sciences, and Duke University, Durham, N.C., are collaborating to replicate the study by Dr. El-Zein and colleagues, according to Dr. Jacobson-Kram.

"If these data are reproducible, it would be very concerning," he said, adding that studies similar to Dr. El-Zein's won't yield results for at least a year.

## KEPPRA® (levetiracetam)

250 mg, 500 mg and 750 mg tablets and 100 mg/mL oral solution

Rx only

Brief summary (for full prescribing information, consult package insert)

**INDICATIONS AND USAGE:** Keppra® (levetiracetam) is indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children 4 years of age and older with epilepsy.

**CONTRAINDICATIONS:** This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in Keppra® tablets or oral solution.

**WARNINGS: Neuropsychiatric Adverse Events:** Adults In adults, Keppra® use is associated with the occurrence of central nervous system adverse events that can be classified into the following categories: 1) somnolence and fatigue, 2) coordination difficulties, and 3) behavioral abnormalities. In controlled trials of adult patients with epilepsy, 14.8% of Keppra®-treated patients reported somnolence, compared to 8.4% of placebo patients. There was no clear dose response up to 3000 mg/day. In a study where there was no titration, about 45% of patients receiving 4000 mg/day reported somnolence. The somnolence was considered serious in 0.3% of the treated patients, compared to 0% in the placebo group. About 3% of Keppra®-treated patients discontinued treatment due to somnolence, compared to 0.7% of placebo patients. In 1.4% of treated patients and in 0.9% of placebo patients the dose was reduced, while 0.3% of the treated patients were hospitalized due to somnolence. In controlled trials of adult patients with epilepsy, 14.7% of treated patients reported asthenia, compared to 9.1% of placebo patients. Treatment was discontinued in 0.8% of treated patients as compared to 0.5% of placebo patients. In 0.5% of treated patients and in 0.2% of placebo patients the dose was reduced. A total of 3.4% of Keppra®-treated patients experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination) compared to 1.6% of placebo patients. A total of 0.4% of patients in controlled trials discontinued Keppra® treatment due to ataxia, compared to 0% of placebo patients. In 0.7% of treated patients and in 0.2% of placebo patients the dose was reduced due to coordination difficulties, while one of the treated patients was hospitalized due to worsening of pre-existing ataxia. Somnolence, asthenia and coordination difficulties occurred most frequently within the first 4 weeks of treatment. In controlled trials of patients with epilepsy, 5 (0.7%) of Keppra®-treated patients experienced psychotic symptoms compared to 1 (0.2%) placebo patient. Two (0.3%) Keppra®-treated patients were hospitalized and their treatment was discontinued. Both events, reported as psychosis, developed within the first week of treatment and resolved within 1 to 2 weeks following treatment discontinuation. Two other events, reported as hallucinations, occurred after 1-5 months and resolved within 2-7 days while the patients remained on treatment. In one patient experiencing psychotic depression occurring within a month, symptoms resolved within 45 days while the patient continued treatment. A total of 13.3% of Keppra® patients experienced other behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability, etc.) compared to 6.2% of placebo patients. Approximately half of these patients reported these events within the first 4 weeks. A total of 1.7% of treated patients discontinued treatment due to these events, compared to 0.2% of placebo patients. The treatment dose was reduced in 0.8% of treated patients and in 0.5% of placebo patients. A total of 0.8% of treated patients had a serious behavioral event (compared to 0.2% of placebo patients) and were hospitalized. In addition, 4 (0.5%) of treated patients attempted suicide compared to 0% of placebo patients. One of these patients successfully committed suicide. In the other 3 patients, the events did not lead to discontinuation or dose reduction. The events occurred after patients had been treated for between 4 weeks and 6 months. **Pediatric Patients:** In pediatric patients, Keppra® is associated with somnolence, fatigue, and behavioral abnormalities. In the double-blind, controlled trial in children with epilepsy, 22.8% of Keppra®-treated patients experienced somnolence, compared to 11.3% of placebo patients. The design of the study prevented accurately assessing dose-response effects. No patient discontinued treatment for somnolence. In about 3.0% of Keppra®-treated patients and in 3.1% of placebo patients the dose was reduced as a result of somnolence. Asthenia was reported in 8.9% of Keppra®-treated patients, compared to 3.1% of placebo patients. No patient discontinued treatment for asthenia, but asthenia led to a dose reduction in 3.0% of Keppra®-treated patients compared to 0% of placebo patients. A total of 37.6% of Keppra®-treated patients experienced behavioral symptoms (reported as agitation, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesia, nervousness, neurosis, and personality disorder), compared to 18.6% of placebo patients. Hostility was reported in 11.9% of Keppra®-treated patients, compared to 6.2% of placebo patients. Nervousness was reported in 9.9% of Keppra®-treated patients, compared to 2.1% of placebo patients. Depression was reported in 3.0% of Keppra®-treated patients, compared to 1.0% of placebo patients. One Keppra®-treated patient experienced suicidal ideation. A total of 3.0% of Keppra®-treated patients discontinued treatment due to psychotic and nonpsychotic adverse events, compared to 4.1% of placebo patients. Overall, 10.9% of Keppra®-treated patients experienced behavioral symptoms associated with discontinuation or dose reduction, compared to 6.2% of placebo patients. **Withdrawal Seizures:** Antiepileptic drugs, including Keppra®, should be withdrawn gradually to minimize the potential of increased seizure frequency.

**PRECAUTIONS: Hematologic Abnormalities:** Adults Minor, but statistically significant, decreases compared to placebo in total mean RBC count ( $0.03 \times 10^6/\text{mm}^3$ ), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in Keppra®-treated patients in controlled trials. A total of 3.2% of treated and 1.8% of placebo patients had at least one possibly significant ( $\leq 2.8 \times 10^9/\text{L}$ ) decreased WBC, and 2.4% of treated and 1.4% of placebo patients had at least one possibly significant ( $\leq 1.0 \times 10^9/\text{L}$ ) decreased neutrophil count. Of the treated patients with a low neutrophil count, all but one rose towards or to baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts. **Pediatric Patients:** Minor, but statistically significant, decreases in WBC and neutrophil counts were seen in Keppra®-treated patients as compared to placebo. The mean decreases from baseline in the Keppra®-treated group were  $-0.4 \times 10^9/\text{L}$  and  $-0.3 \times 10^9/\text{L}$ , respectively, whereas there were small increases in the placebo group. Mean relative lymphocyte counts increased by 1.7% in Keppra®-treated patients, compared to a decrease of 4% in placebo patients (statistically significant). In the well-controlled trial, more Keppra®-treated patients had a possibly clinically significant abnormally low WBC value (3.0% Keppra®-treated versus 0% placebo), however, there was no apparent difference between treatment groups with respect to neutrophil count (5.0% Keppra®-treated versus 4.2% placebo). No patient was discontinued secondary to low WBC or neutrophil counts. **Hepatic Abnormalities:** There were no meaningful changes in mean liver function tests (LFT) in controlled trials in adult and pediatric patients; lesser LFT abnormalities were similar in drug and placebo-treated patients in controlled trials (1.4%). No adult or pediatric patients were discontinued from controlled trials for LFT abnormalities except for 1 (0.07%) adult epilepsy patient receiving open treatment. **Information For Patients:** Patients should be instructed to take Keppra® only as prescribed. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised that Keppra® may cause dizziness and somnolence. Accordingly, patients should be advised not to drive or operate machinery or engage in other hazardous activities until they have gained sufficient experience on Keppra® to gauge whether it adversely affects their performance of these activities. Physicians should advise patients and caregivers to read the patient information leaflet which appears as the last section of the labeling. **Laboratory Tests:** Although most laboratory tests are not systematically altered with Keppra® treatment, there have been relatively infrequent abnormalities seen in hematologic parameters and liver function tests. **Drug Interactions:** In vitro data on metabolic interactions indicate that Keppra® is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above  $C_{max}$  levels achieved within the therapeutic dose range, are neither inhibitors of nor high affinity substrates for human liver cytochrome P450 isozymes, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid. Levetiracetam circulates largely unbound ( $<10\%$  bound) to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely. Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic studies (phenytoin, valproate, oral contraceptive, digoxin, warfarin, probenecid) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients. **Drug-Drug Interactions Between Keppra® and Other Antiepileptic Drugs (AEDs):** Phenytoin: Keppra® (3000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy. Pharmacokinetics of levetiracetam were also not affected by phenytoin. **Valproate:** Keppra® (1500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers. Valproate 500 mg twice daily did not modify the rate or extent of levetiracetam absorption or its plasma clearance or urinary excretion. There also was no effect on exposure to and the excretion of the primary metabolite, ucb L057. Potential drug interactions between Keppra® and other AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone and valproate) were also assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data indicate that levetiracetam does not influence the plasma concentration of other AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam. **Effect of AEDs in Pediatric Patients:** There was about a 22% increase of apparent total body clearance of levetiracetam when it was co-administered with enzyme-inducing AEDs. Dose adjustment is not recommended. Levetiracetam had no effect on plasma concentrations of carbamazepine, valproate, topiramate, or lamotrigine. **Other Drug Interactions:** Oral Contraceptives: Keppra® (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that impairment of contraceptive efficacy is unlikely. Coadministration of this oral contraceptive did not influence the pharmacokinetics of levetiracetam. **Digoxin:** Keppra® (1000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam. **Warfarin:** Keppra® (1000 mg twice daily) did not influence the pharmacokinetics of R and S warfarin. Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam. **Probenecid:** Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily.  $C_{max}$  of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal

clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of Keppra® on probenecid was not studied. **Pregnancy: Pregnancy Category C:** In animal studies, levetiracetam produced developmental toxicity at doses similar to or greater than human therapeutic doses. Administration to female rats throughout pregnancy and lactation was associated with increased incidences of minor fetal skeletal abnormalities and retarded offspring growth pre- and/or postnatally at doses  $\geq 350$  mg/kg/day (approximately equivalent to the maximum recommended human dose of 3000 mg [MRHD] on a mg/m<sup>2</sup> basis) and with increased pup mortality and offspring behavioral alterations at a dose of 1800 mg/kg/day (6 times the MRHD on a mg/m<sup>2</sup> basis). The developmental no effect dose was 70 mg/kg/day (0.2 times the MRHD on a mg/m<sup>2</sup> basis). There was no overt maternal toxicity at the doses used in this study. Treatment of pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and increased incidences of minor fetal skeletal abnormalities at doses  $\geq 600$  mg/kg/day (approximately 4 times MRHD on a mg/m<sup>2</sup> basis) and in decreased fetal weights and increased incidences of fetal malformations at a dose of 1800 mg/kg/day (12 times the MRHD on a mg/m<sup>2</sup> basis). The developmental no effect dose was 200 mg/kg/day (1.3 times the MRHD on a mg/m<sup>2</sup> basis). Maternal toxicity was also observed at 1800 mg/kg/day. When pregnant rats were treated during the period of organogenesis, fetal weights were decreased and the incidence of fetal skeletal variations was increased at a dose of 3600 mg/kg/day (12 times the MRHD). 1200 mg/kg/day (4 times the MRHD) was a developmental no effect dose. There was no evidence of maternal toxicity in this study. Treatment of rats during the last third of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m<sup>2</sup> basis). There are no adequate and well-controlled studies in pregnant women. Keppra® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Keppra® Pregnancy Registry:** UCB Pharma, Inc. has established the Keppra® Pregnancy Registry to advance scientific knowledge about safety and outcomes associated with pregnant women being treated with Keppra®. To ensure broad program access and reach, either a healthcare provider or the patient can initiate enrollment in the Keppra® Pregnancy Registry by calling (888) 537-7734 (toll free). Patients may also enroll in the North American Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free). **Labor And Delivery:** The effect of Keppra® on labor and delivery in humans is unknown. **Nursing Mothers:** Levetiracetam is excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants from Keppra®, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in patients below 4 years of age have not been established. Studies of levetiracetam in juvenile rats (dosing from day 4 through day 52 of age) and dogs (dosing from week 3 through week 7 of age) at doses of up to 1800 mg/kg/day (approximately 7 and 24 times, respectively, the maximum recommended pediatric dose of 60 mg/kg/day on a mg/m<sup>2</sup> basis) did not indicate a potential for age-specific toxicity. **Geriatric Use:** Of the total number of subjects in clinical studies of levetiracetam, 347 were 65 and over. No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of Keppra® in these patients. A study in 16 elderly subjects (age 61-88 years) with oral administration of single dose and multiple twice-daily doses for 10 days showed no pharmacokinetic differences related to age alone. Levetiracetam is known to be substantially excreted by the kidney, 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. **Use In Patients With Impaired Renal Function:** Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance. Caution should be taken in dosing patients with moderate and severe renal impairment and in patients undergoing hemodialysis. The dosage should be reduced in patients with impaired renal function receiving Keppra® and supplemental doses should be given to patients after dialysis (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION, Adult Patients with Impaired Renal Function in package insert).

**ADVERSE REACTIONS:** In well-controlled clinical studies in adults, the most frequently reported adverse events associated with the use of Keppra® in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, infection and dizziness. In the well-controlled pediatric clinical study, the adverse events most frequently reported with the use of Keppra® in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, accidental injury, hostility, nervousness, and asthenia. Table 1 lists treatment-emergent adverse events that occurred in at least 1% of adult epilepsy patients treated with Keppra® participating in placebo-controlled studies and were numerically more common than in patients treated with placebo. Table 2 lists treatment-emergent adverse events that occurred in at least 2% of pediatric epilepsy patients (ages 4-16 years) treated with Keppra® participating in the placebo-controlled study and were numerically more common than in pediatric patients treated with placebo. In these studies, either Keppra® or placebo was added to concurrent AED therapy. Adverse events were usually mild to moderate in intensity. The prescriber should be aware that these figures, obtained when Keppra® was added to concurrent AED therapy, cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidence in the population studied. **Table 1: Incidence (%) Of Treatment-Emergent Adverse Events In Placebo-Controlled, Add-On Studies, In Adults By Body System (Adverse Events Occurred In At Least 1% Of Keppra®-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients).** Keppra® (N=769) vs Placebo (N=439): **Body System/Adverse Event: Body as a Whole:** Asthenia (15% vs 9%); Headache (14% vs 13%); Infection (13% vs 8%); Pain (7% vs 6%); **Digestive System:** Anorexia (3% vs 2%); **Nervous System:** Amnesia (2% vs 1%); Anxiety (2% vs 1%); Ataxia (3% vs 1%); Depression (4% vs 2%); Dizziness (9% vs 4%); Emotional Lability (2% vs 0%); Hostility (2% vs 1%); Nervousness (4% vs 2%); Paresthesia (2% vs 1%); Somnolence (15% vs 8%); Vertigo (3% vs 1%). **Respiratory System:** Cough Increased (2% vs 1%); Pharyngitis (6% vs 4%); Rhinitis (4% vs 3%); Sinusitis (2% vs 1%). **Special Senses:** Diplopia (2% vs 1%). Other events reported by 1% or more of adult patients treated with Keppra® but as or more frequent in the placebo group were the following: abdominal pain, accidental injury, amblyopia, arthralgia, back pain, bronchitis, chest pain, confusion, constipation, convulsion, diarrhea, drug level increased, dyspepsia, ecchymosis, fever, flu syndrome, fungal infection, gastroenteritis, gingivitis, grand mal convulsion, insomnia, nausea, otitis media, rash, thinking abnormal, tremor, urinary tract infection, vomiting and weight gain. **Table 2: Incidence (%) Of Treatment-Emergent Adverse Events In A Placebo-Controlled, Add-On Study In Pediatric Patients Ages 4-16 Years By Body System (Adverse Events Occurred In At Least 2% Of Keppra®-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients).** Keppra® (N=101) vs Placebo (N=97): **Body System/Adverse Event: Body as a Whole:** Accidental Injury (17% vs 10%); Asthenia (9% vs 3%); Pain (6% vs 3%); Flu Syndrome (3% vs 2%); Face Edema (2% vs 1%); Neck Pain (2% vs 1%); Viral Infection (2% vs 1%). **Digestive System:** Vomiting (15% vs 13%); Anorexia (13% vs 8%); Diarrhea (8% vs 7%); Gastroenteritis (4% vs 2%); Constipation (3% vs 1%). **Hemic and Lymphatic System:** Ecchymosis (4% vs 1%). **Metabolic and Nutritional:** Dehydration (2% vs 1%). **Nervous System:** Somnolence (23% vs 11%); Hostility (12% vs 6%); Nervousness (10% vs 2%); Personality Disorder (8% vs 7%); Dizziness (7% vs 2%); Emotional Lability (6% vs 4%); Agitation (6% vs 1%); Depression (3% vs 1%); Vertigo (3% vs 1%); Reflexes Increased (2% vs 1%); Confusion (2% vs 0%). **Respiratory System:** Rhinitis (13% vs 8%); Cough Increased (11% vs 7%); Pharyngitis (10% vs 8%); Asthma (2% vs 1%). **Skin and Appendages:** Pruritus (2% vs 0%); Skin Discoloration (2% vs 0%); Vesiculobullous Rash (2% vs 0%). **Special Senses:** Conjunctivitis (3% vs 2%); Amblyopia (2% vs 0%); Ear Pain (2% vs 0%). **Urogenital System:** Albuminuria (4% vs 0%); Urine Abnormality (2% vs 1%). Other events occurring in 2% or more of pediatric patients treated with Keppra® but as or more frequent in the placebo group were the following: abdominal pain, allergic reaction, ataxia, convulsion, epistaxis, fever, headache, hyperkinesia, infection, insomnia, nausea, otitis media, rash, sinusitis, status epilepticus (not otherwise specified), thinking abnormal, tremor, and urinary incontinence. **Time Course Of Onset Of Adverse Events:** Of the most frequently reported adverse events in adults, asthenia, somnolence and dizziness appeared to occur predominantly during the first 4 weeks of treatment with Keppra®. **Discontinuation Or Dose Reduction In Well-Controlled Clinical Studies:** In well-controlled clinical studies, 15.0% of patients receiving Keppra® and 11.6% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. Table 3 lists the most commonly (>1%) adverse events that resulted in discontinuation or dose reduction. **Table 3: Adverse Events That Most Commonly Resulted In Discontinuation Or Dose Reduction In Placebo-Controlled Studies In Adult Patients With Epilepsy.** Keppra® (N=769) vs Placebo (N=439): [Number (%); Asthenia [10 (1.3%) vs 3 (0.7%)]; Convulsion [23 (3.0%) vs 15 (3.4%)]; Dizziness [11 (1.4%) vs 0]; Somnolence [34 (4.4%) vs 7 (1.6%)]; Rash [0 vs 5 (1.1%)]. In the well-controlled pediatric clinical study, 16.8% of patients receiving Keppra® and 20.6% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. The adverse events most commonly associated ( $\geq 3\%$  in patients receiving Keppra®) with discontinuation or dose reduction in the well-controlled study are presented in Table 4. **Table 4: Adverse Events Most Commonly Associated With Discontinuation Or Dose Reduction In The Placebo-Controlled Study In Pediatric Patients Ages 4-16 Years With Epilepsy.** Keppra® (N=101) vs Placebo (N=97): [Number (%); Somnolence [3 (3.0%) vs 3 (3.1%)]; Hostility [7 (6.9%) vs 2 (2.1%)]; Asthenia [3 (3.0%) vs 0 (0.0%)]. **Comparison Of Gender, Age And Race:** The overall adverse experience profile of Keppra® was similar between females and males. There are insufficient data to support a statement regarding the distribution of adverse experience reports by age and race. **Postmarketing Experience:** In addition to the adverse experiences listed above, the following have been reported in patients receiving marketed Keppra® worldwide. The listing is alphabetized: leukopenia, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases) and thrombocytopenia. Alopecia has been reported with Keppra® use; recovery was observed in the majority of cases where Keppra® was discontinued. There have been reports of suicidal behavior (including completed suicide) with marketed Keppra®. These adverse experiences have not been listed above, and data are insufficient to support an estimate of their incidence or to establish causation.

