

# Lacking Alternatives, MDs Stick With Atypicals

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MADRID — Prescriptions for atypical antipsychotics have not decreased significantly among elderly patients with dementia, despite the black box warning of an increased risk of death associated with the drugs, according to Henry Riordan, Ph.D., speaking at the 10th International Conference for Alzheimer's Disease and Related Disorders.

Overall, prescribing has declined only 2.4%, even though the number of new prescriptions issued has decreased by 37%, Dr. Riordan said at the meeting presented by the Alzheimer's Association.

This pattern probably reflects physicians' perceptions that the clinical benefits of the drugs outweigh their well-documented risks for older dementia patients with serious behavioral issues.

More than 80% of Alzheimer's patients will eventually develop psychotic symp-

toms, said Dr. Riordan, vice president and global head of medical and scientific affairs for I3 Research in Basking Ridge, N.J. "These are the issues that typically result in institutionalization and take a big chunk out of these patients' quality of life," he said in an interview.

The problem lands patients, families, and physicians on the horns of a very sharp dilemma. "Withholding the drugs is dangerous, especially when you are dealing with behavior that can be either self-

injurious or harmful to caregivers," Dr. Riordan said, but the risks of atypical antipsychotics were well documented years before the Food and Drug Administration's warning.

Fifteen of the 17 randomized atypical antipsychotic trials the FDA reviewed found a significantly increased risk of death—usually cardiovascular or infectious—among elderly, demented patients taking the drugs, compared with placebo. The resultant black box warning highlighted the danger and reiterated that the drugs are not approved for the treatment of patients with dementia-related psychosis.

To estimate the impact of the black box warning on prescribing patterns, Dr. Riordan examined claims data from a large U.S. health plan, for 10 months before and 10 months after the 2005 warning was issued. The database included 900,000 people older than 65 years of age; 20,515 had a diagnosis of dementia. Of those, 5,000 were taking at least one atypical antipsychotic before the black box warning.

Ten months after the warning, 4,883 people were still taking the drugs. New prescriptions had decreased significantly, however, declining from 3,423 to 2,148. "This probably tells us that if you were on the drug, you stayed on it, but that physicians might have been looking at something else for patients with new symptoms."

A supporting pattern emerged when Dr. Riordan broke down the data by age: Prescriptions decreased more among patients younger than 81 (5%) than they did among older patients (0.73%). "Here we're probably seeing a risk-benefit ratio that's perceived as different for older people," Dr. Riordan said.

"If someone has been on it with good efficacy, it would probably just be continued. But the physician's thought process might be very different for someone younger, in the earlier stages of the disease," according to Dr. Riordan.

Among the six drugs included in the study (aripiprazole, clozapine, ziprasidone, risperidone, quetiapine, and olanzapine), only two showed significant pre- and post-warning prescribing changes. Prescriptions for quetiapine increased significantly, while those for olanzapine decreased significantly.

"It could be that quetiapine is being used more now for its sedative effect in sleep difficulty, and clozapine less due to its issues with increasing cardiovascular risk factors."

Dr. Riordan now is investigating whether the decrease in new prescriptions caused any similar increases in prescriptions for alternative treatments, like mood stabilizers or antianxiolytics.

## KEPPRA® (levetiracetam)

250 mg, 500 mg, 750 mg, and 1000 mg tablets, and 100 mg/ml oral solution

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

Rx only

**INDICATIONS AND USAGE:** KEPPRA 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 completed 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. See ADVERSE REACTIONS, Postmarketing Experience section for events reported with marketed KEPPRA. **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 the 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. See ADVERSE REACTIONS, Postmarketing Experience section for events reported with marketed KEPPRA. 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 ( $\leq 2.8 \times 10^6/\text{L}$ ) decreased WBC, and 2.4% of treated and 1.4% of placebo patients had at least one possibly significant ( $\leq 1.0 \times 10^6/\text{L}$ ) 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  $-0.4 \times 10^6/\text{L}$  and  $-0.3 \times 10^6/\text{L}$ , 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. See ADVERSE REACTIONS, Postmarketing Experience section for events reported with marketed KEPPRA. **Hepatic Abnormalities:** There were no meaningful changes in mean liver function tests (LFT) in controlled trials in adult or 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. See ADVERSE REACTIONS, Postmarketing Experience section for events reported with marketed KEPPRA. **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  $C_{50}$  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 was also 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.  $C_{50}$ 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.

**Carcinogenesis, Mutagenesis, Impairment Of Fertility: Carcinogenesis:** Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day. The highest dose corresponds to 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on a  $\text{mg}/\text{m}^2$  basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. A study was

conducted in which mice received levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960 mg/kg/day (high dose is equivalent to 2 times the MRHD on a  $\text{mg}/\text{m}^2$  or exposure basis). Although no evidence for carcinogenicity was seen, the potential for a carcinogenic response has not been fully evaluated in that species because adequate doses have not been studied. **Mutagenesis:** Levetiracetam was not mutagenic in the Ames test or in mammalian cells *in vitro* in the Chinese hamster ovary/HGPRT locus assay. It was not clastogenic in an *in vitro* analysis of metaphase chromosomes obtained from Chinese hamster ovary cells or in an *in vivo* mouse micronucleus assay. The hydrolysis product and major human metabolite of levetiracetam (ucb L057) was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay. **Impairment Of Fertility:** No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day (approximately 6 times the maximum recommended human dose on a  $\text{mg}/\text{m}^2$  or exposure basis). **Pregnancy: Pregnancy Category C:** In animal studies, levetiracetam produced evidence of 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  $\text{mg}/\text{m}^2$  basis) and with increased pup mortality and offspring behavioral alterations at a dose of 1800 mg/kg/day (6 times the MRHD on a  $\text{mg}/\text{m}^2$  basis). The developmental no effect dose was 70 mg/kg/day (0.2 times the MRHD on a  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{m}^2$  basis). The developmental no effect dose was 200 mg/kg/day (1.3 times the MRHD on a  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{m}^2$  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, 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  $\text{mg}/\text{m}^2$  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).

**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 incidences 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, dyspnea, 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=1011) 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 1%); 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 common (>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=1011) 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: abnormal liver function test, hepatitis, leukopenia, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), thrombocytopenia and weight loss. Alopecia has been reported with KEPPRA use; recovery was observed in 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.



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