Levetiracetam: Part II, the Clinical Profile of a Novel Anticonvulsant Drug

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ABSTRACT

The objective of this article was to review and summarize the available reports on the profile of the novel anticonvulsant drug levetiracetam (LEV) in a clinical setting. Therefore, a careful search was conducted in the MEDLINE database and combined with guidelines from regulatory agencies, proceedings of professional scientific meetings, and information provided by the manufacturers. This article is devoted to the clinical pharmacology and clinical trials of LEV investigating its efficacy and safety as add-on therapy or monotherapy for various seizure types. Finally, results from postmarketing surveillance of LEV are briefly discussed. In general, LEV is shown to be a safe, broad-spectrum anticonvulsant drug with highly beneficial pharmacokinetic properties, a favorable long-term retention rate, and a high responder rate, indicating that LEV is an efficient therapeutic option for the treatment of several types of epilepsy.

CLINICAL PHARMACOLOGY

Levetiracetam (LEV) is a white to off-white powder with a bitter taste and faint odor that is highly soluble in water (0.104 g/mL). It is structurally unrelated to other anticonvulsant drugs (ACDs), with an empirical formula of $C_8H_{14}N_2O_2$ and a molecular weight of 170.21.

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Dosage and Administration

LEV is available as film-coated tablets containing 250, 500, 750, and 1000 mg of LEV, although not all tablet forms are available in every country (Patsalos 2004). LEV can be ingested without regard to meal times: The time at which peak concentrations occur in serum ($T_{\max}$) is delayed slightly but the maximum concentration ($C_{\max}$) is unaffected by food intake (Patsalos 2000, 2004). Patients who do not become seizure-free at the lowest recommended dose of LEV (1000 mg/day) should be up-titrated to 2000 mg/day or 3000 mg/day to provide the greatest chance for seizure freedom with little or no increased risk for adverse events (Meencke and Buyle 2006). LEV treatment is usually started at 500 mg twice daily and increased in two-weekly steps of 1000 mg/day to 3000 mg/day (Patsalos 2004). Reports indicate that the target range for daily dosage of 1000–3000 mg is 35–120 $\mu\text{mol/L}$ (Patsalos 2000). A study by Grant and Shorvon (2000) has shown that 1000 mg stepwise addition of LEV is well tolerated up to a dosage of 4000 mg/day, at which there is an increased incidence of somnolence and asthenia. In fact, dose escalation above 3000 mg/day should be done only after careful analyses of the risk–benefit ratio, due to a higher risk for adverse effects apparent from several studies (e.g., Genton et al. 2006).

A liquid formulation (LEV 100 mg/mL) for oral ingestion has been developed for those patients with difficulties in swallowing. In 2006, an intravenous (i.v.) LEV formulation was approved for use as adjunctive therapy in the treatment of epilepsy by both the Food and Drug Administration (FDA) and the European Agency for Evaluation of Medicinal Products (EMA). LEV administered by i.v. infusion is indicated in emergency situations and appears to be well tolerated in healthy subjects, with a pharmacokinetic profile and bioequivalence consistent with that of LEV administered orally (Ramael et al. 2006a, 2006b). The i.v. formulation is provided in 5-mL glass vials containing 500 mg LEV (LEV 100 mg/mL), which should be infused over 15 min according to EMA guideline EMA/H/C/277/X/46. Finally, an extended release formulation of LEV, Keppra XR, is being developed by UCB, and a double-blind study as well as an open-label trial with Keppra XR in partial-onset seizures will start enlisting patients as of April and May 2007, respectively (NIH clinical trial register).

Absorption and Distribution

LEV is rapidly and almost completely (>95%) absorbed following oral ingestion with $T_{\max}$ occurring at 1.3–5.2 h (Edwards et al. 2004; Patsalos 2004). LEV displays dose-linearity in the therapeutic range of 500–5000 mg and predictable, dose-proportional pharmacokinetics with steady state in serum levels occurring within 24–48 h after initiation of therapy (Patsalos 2004). The mean half-life ($t_{1/2}$) of LEV in serum is 6–13.3 h (Edwards et al. 2004; Patsalos 2004).

LEV readily enters the cerebrospinal fluid (CSF) compartment with a $T_{\max}$ of 3–7.3 h (Edwards et al. 2004; Patsalos 2004). Interestingly, the mean $t_{1/2}$ of LEV in CSF is 24 h, showing that the efflux of LEV from the CNS compartment is twice as long as that from the blood (Edwards et al. 2004). This is in agreement with clinical observations of prolonged anticonvulsant activity even when LEV serum concentrations are reported to be low (Kasteleijn-Nolst et al. 1996; Sohn et al. 2001). LEV seems to have a prolonged duration of action, supporting a twice-daily dosing strategy (Patsalos 2004).

Metabolism, Excretion, and Elimination

Metabolism of LEV is minimal, and excretion occurs almost completely through the urinary system (Patsalos 2000, 2004). Approximately 34% of the administered dose of LEV is metabolized (not involving the hepatic cytochrome P450 [CYP] system) and 66% is recovered unchanged in urine (Patsalos 2000, 2004). LEV is rapidly cleared by the kidneys proportional to creatinine clearance, with >90% of the drug being excreted within 48 h. It is filtered by the glomeruli and is subjected to partial tubular reabsorption (Patsalos 2000, 2004).

Metabolism occurs mainly in blood, where an amidase hydrolyzes LEV to a pharmacologically inactive metabolite. Overall, no significant differences in pharmacokinetics between sexes or races have been reported, although some special populations require extra care (Patsalos 2004).

Special Populations

Dosage of LEV should be adjusted for some special populations. In children, renal clearance is higher and dosage should be increased to approximately 130% of the adult dose on a per kg of body weight basis (French 2001; Pellock et al. 2001; Patsalos 2004).

Elderly people often show a reduction in renal clearance and dosage should be lowered accordingly. Likewise, in patients showing renal impairment or suffering from hepatorenal syndrome, dosage reduction should be considered (French 2001).

LEV and other ACDs that do not induce cytochrome P450 enzymes are not expected to interact with oral contraceptives (Harden and Leppik 2006). This was confirmed in an earlier report, in which LEV did not affect the pharmacokinetics or efficacy of an oral contraceptive containing ethinyl estradiol and levonorgestrel (Ragueneau-Majlessi et al. 2002). Pregnant women undergo a variety of physiological changes including increased hepatic metabolism, decreased plasma protein binding, and fluctuating hormone levels. Renal functioning increases during pregnancy, meaning that plasma concentrations of drugs that are excreted by kidneys, like LEV, could decrease, and dose adjustment may be required (French 2001; McAuley and Anderson 2002).

Pharmacokinetic and Pharmacodynamic Drug Interactions

Few pharmacokinetic drug interactions with LEV have been reported (Patsalos 2004). Meta-analysis revealed that LEV does not affect the concentrations of carbamazepine (CBZ), clobazam (CLB), clonazepam (CNZ), diazepam (DZP), gabapentin (GPT), lamotrigine (LTG), phenytoin (PHT), phenobarbital (PHB), primidone (PRM), valproic acid (VPA), vigabatrin (VGB), and ethosuximide (ETS) (Kasteleijn-Nolst et al. 1996; Perucca et al. 2000). Conversely, PHT, mesuximide (MSM), CBZ, and oxcarbazepine (OXZ) have been shown to lower LEV concentrations, while VPA minimally affected them (May et al. 2003). Enzyme-inducing ACDs may increase the clearance of LEV by about 20–30%, but a high variability has to be considered (May et al. 2003; Perucca et al. 2003).

Corroborating some of the results obtained in laboratory animals, several pharmacodynamic interactions with LEV have been described in clinical practice. Negative pharmacodynamic interactions have been reported with both CBZ and topiramate (TPM). Sisodiya

and Glauser and their respective colleagues provided anecdotal evidence that the add-on use of LEV could result in increased symptomatic CBZ or TPM neurotoxicity (Glauser et al. 2002; Sisodiya et al. 2002). Kelly and colleagues have reported that in their clinical experience, the most frequently discontinued combinations due to adverse effects are those of LEV with CBZ or LTG (Kelly et al. 2004).

CLINICAL TRIALS

The year 2006 has seen several milestone changes in the indications for LEV (Keppra®) in either the U.S.A. or Europe. LEV has been granted European monotherapy approval for partial seizures. In the U.S.A. and Europe, oral and intravenous formulations of LEV were approved as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. Just recently, a positive opinion was issued recommending that the European Commission grant a marketing authorization for LEV as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures. As of January 2007, the EMEA guidelines state that LEV is indicated:

- 1) As monotherapy in the treatment of partial-onset seizures with or without secondary generalization in patients from 16 years of age with newly diagnosed epilepsy,
- 2) As adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults and children from four years of age with epilepsy,
- 3) As adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy (JME), and
- 4) As adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalized epilepsy (IGE).

For reasons discussed in the following, in the U.S.A. the FDA did not yet approve LEV as monotherapy in the treatment of partial onset seizures or as an adjunctive therapy in the treatment of primary generalized tonic-clonic seizures.

Pivotal Trials of LEV in Partial-Onset Seizures

A clinical development plan normally includes several phase III studies, some of which may address special issues (e.g., effects on cognitive function and cognitive outcome; efficacy and tolerability in special groups, such as children, the elderly, or cognitively impaired patients) (Arroyo et al. 2004). The pivotal trial leading toward registration will be an adjunctive therapy trial in refractory partial seizures (Arroyo et al. 2004). Both the FDA and the EMEA are likely to grant approval for use of LEV as an adjunctive therapy for partial epilepsy after at least two adequate and well-controlled trials (Arroyo et al. 2004).

At least four multicenter, double-blind placebo-controlled studies have shown the safety and effectiveness of LEV add-on therapy for refractory partial epilepsy in a clinical setting. These studies used comparable inclusion criteria, selecting male and female adult patients suffering from refractory partial seizures (with or without secondary generalization) that were on a stable regimen of one or two concomitant ACDs and had a stable and reasonable

number of seizures. In general, outcome measures were comparable among the studies: the reduction in (weekly) seizure frequency was usually the primary outcome measure and the percentage of responders was usually chosen as the secondary efficacy parameter (according to the Committee for Human Medicinal Products [CHMP] of the EMEA, this refers to the proportion of patients experiencing a reduction in seizure frequency of at least 50% when comparing baseline recordings to the treatment period). Safety and tolerability were reported in all trials and are discussed in detail later. Three studies (N132, N138, and N052) were parallel trials and one (N051) was a crossover trial.

Shorvon and colleagues (Study N051) conducted their 32-week crossover study in 62 centers in Europe (Shorvon et al. 2000). A large group of patients ($n = 324$) was distributed across a placebo group, an LEV 1000 mg/day group, or an LEV 2000 mg/day group. In the 1000 mg/day and 2000 mg/day LEV-treated groups, seizure frequency was reduced by 17.1% and 21.4%, respectively ($p \leq 0.001$ for either dose vs. placebo), with responder rates of 20.8% and 35.2% (compared to 6.3% in the placebo group, $p \leq 0.001$ for either dose) (Shorvon et al. 2000). The withdrawal rate was limited throughout the experiment: 7.5% and 14.2% the 2000 mg/day in LEV 1000mg/day and groups, respectively withdrew from the study because of one or more adverse events, compared to 5.4% in the placebo group (Shorvon et al. 2000). The incidence of serious adverse events possibly related to the test drug were 2.7% with placebo, 1.9% in the LEV 1000 mg/day group, and 7.5% in the LEV 2000 mg/day group (Shorvon et al. 2000). In general, there were no significant differences in the incidence of adverse events for either LEV-treated group as compared to placebo, although somnolence, asthenia, and headache were seen more often in patients receiving LEV (Table 1) (Shorvon et al. 2000).

The crossover part of this study was elaborated on further by Boon and colleagues (Boon et al. 2002). Their study provided additional information on dose–response relationship and on withdrawal effects, showing that LEV displayed dose-dependent effects (the dose of 2000 mg/day was more effective than 1000 mg/day) and demonstrating a lack of typical withdrawal-related adverse events or rebound phenomena after withdrawal or down-titration of the drug (Boon et al. 2002).

Betts and colleagues (Study N052) started a 24-week study in 37 sites in Belgium and the UK (Betts et al. 2000). Although safety and tolerability were the primary outcome measures, the efficacy of LEV at 2000 mg/day and at 4000 mg/day was compared to that of placebo in patients with either partial or primary generalized refractory epilepsy ($n = 119$). The median reductions in seizure frequency were 41.2% or 66.7% in the LEV 2000 mg/day group and 43.4% or 46.8% in the LEV 4000 mg/day group (partial or generalized seizures, respectively) (Betts et al. 2000). These differences were not significant compared to placebo (Betts et al. 2000). After 24 weeks of treatment, responder rates of 48.1% and 28.6% (2000 mg/day and 4000 mg/day, respectively) were reported, compared to 16.1% in the placebo group ($p = 0.01$ for the LEV 2000 mg daily treatment group compared to placebo) (Betts et al. 2000). Adverse events were reported in 83.3% of the LEV 2000 mg/day group, in 84.2% of the LEV 4000 mg/day group, and in 84.6% of the placebo group (Betts et al. 2000). The most frequently reported adverse events were somnolence and asthenia (Table 1). The somnolence was most commonly seen in the LEV 4000 mg/day group; the incidence was comparable between the LEV 2000 mg/day and the placebo groups. Asthenia was more often reported in the LEV 2000 mg/day group, but its incidence was similar in the LEV 4000 mg/day and the placebo groups (Betts et al. 2000). Other frequently reported adverse events were accidental injury (most frequent in the placebo

TABLE 1. Most frequently reported adverse events during large clinical trials with LEV.

Study	Treatment	Accidental injury %	Asthenia %	Dizziness %	Headache %	Infection %	Nausea %	Somnolence %
Shorvon et al. 2000	Placebo	15.2	8.0	3.6	8.9	6.3	4.5	4.5
	LEV 1000 mg/day	12.3	7.5	4.7	13.2	9.4	5.7	9.4
	LEV 2000 mg/day	13.2	31.2	6.6	16.0	6.6	2.8	11.3
Betts et al. 2000	Placebo	15.4	15.4	×	×	7.7	2.6	25.6
	LEV 2000 mg/day	2.4	31.0	4.8	×	2.4	×	26.2
	LEV 4000 mg/day	13.2	13.2	10.5	×	15.8	13.2	44.7
Cereghino et al. 2000	Placebo	24.2	11.6	7.4	20.0	12.6	×	13.7
	LEV 1000 mg/day	16.3	16.3	17.3	21.4	27.6	×	20.4
	LEV 3000 mg/day	12.9	12.9	19.8	20.8	26.7	×	18.8
Ben-Menachem and Falter 2000	Placebo	9.5	6.7	×	10.5	3.8	×	3.8
	LEV 3000 mg/day	2.2	13.8	×	3.3	7.2	×	6.1
Glauser et al. 2006	Placebo	10.0	3.0	2.0	×	×	×	11.0
	LEV 60 mg/kg/day	17.0	9.0	7.0	×	×	×	23.0
Ben-Menachem et al. 2003	LEV 3000 mg/day (median dose)	28.0	22.6	18.9	25.8	26.6	9.1	23.0
	LEV 1000, 2000, or 3000 mg/day	×	8.3	7.2	5.9	×	×	12.8
Genton et al. 2006	LEV 2000 mg/day (median dose)	×	19.2	9.7	11.2	×	×	16.7
	CBZ 434.1 mg/day	×	14.1	13.7	25.4	×	10.7	9.3
Ben-Menachem et al. 2006	LEV 1170.4 mg/day (mean dose)	×	16.5	10.9	20.7	×	7.0	11.2
	Placebo	×	×	×	23.3	×	×	×
Verdru et al. 2005	LEV 2935 mg/day (mean dose)	×	6.5	10.2	23.3	×	×	13.9

group), infection, nausea, dizziness, and urinary tract infection (Table 1) (Betts et al. 2000). Serious adverse events were 7.7% in the placebo group, 7.1% in the LEV 2000 mg/day group, and 10.5% in the LEV 4000 mg/day group, but none of these events was considered to be related to the drug treatment (Betts et al. 2000). In general, the incidence of adverse events was not significantly different between treatment groups (Betts et al. 2000).

Another pivotal trial was performed by Cereghino and colleagues (Study N132). It was a 38-week study conducted at 41 sites in the U.S.A. (Cereghino et al. 2000). A large cohort of patients with refractory partial epilepsy ($n = 294$) was randomly distributed over either a placebo, an LEV 1000 mg/day group, or an LEV 3000 mg/day group. Again, promising results were obtained, showing highly significant reductions in seizure frequency of 26.1% and 30.1% for LEV 1000 mg/day and LEV 3000 mg/day, respectively ($p \leq 0.001$ for both doses versus placebo). Responder rates were 37.1% and 39.6% for LEV 1000 mg/day and LEV 3000 mg/day, respectively, compared to 7.4% for placebo ($p \leq 0.001$ for both doses versus placebo). One or more adverse events were reported by 88.4% of patients in the placebo group, 88.8% in the LEV 1000 mg/day group, and 89.1% in the LEV 3000 mg/day group. Withdrawal rates due to adverse events were low: only 5.3% in placebo-treated patients, 6.1% in the LEV 1000 mg/day group, and 6.9% in the LEV 3000 mg/day group. The withdrawals were mostly due to increased somnolence. Other frequent adverse events more commonly reported in the LEV-treated groups were infection, headache, dizziness, asthenia, rhinitis, and flu syndrome, whereas accidental injury was seen more frequently in the placebo group (Table 1). Serious adverse events were 10.5% in the placebo group, 7.1% in the LEV 1000 mg/day group, and 2.0% in the LEV 3000 mg/day group. Again, no statistically significant differences were found between the incidence of adverse effects in placebo-treated and LEV-treated patients (Cereghino et al. 2000).

Ben Menachem and Falter (Study N138) conducted their phase III study in 47 centers in Europe (Ben Menachem and Falter 2000). A total of 286 patients were randomly distributed over a placebo or a LEV 3000 mg/day groups. A highly significant reduction in seizure frequency of 23% was found in the 3000 mg/day LEV-group ($p \leq 0.001$ compared to placebo). The reported responder rate for LEV 3000 mg/day was 39.4%, compared to 14.4% for placebo-treated patients ($p \leq 0.001$). In patients who experienced improved seizure control under add-on treatment, LEV was also evaluated as monotherapy. As in the previously described studies, LEV was in general well tolerated and the incidence of adverse events was low and similar between LEV-treated patients and the placebo-treated group (Table 1). Mild to moderate asthenia and somnolence were the most frequently reported adverse events; they rarely led to drug discontinuation.

Several analyses on the pooled data from the regulatory trials are available. Results of the retrospective analyses vary depending on the inclusion criteria used, but they all clearly show the beneficial effects of LEV add-on therapy in refractory partial epilepsy.

A pooled efficacy analysis by Privitera (2001) demonstrated that patients receiving LEV showed a median decrease in partial seizures of 31.3% compared to baseline ($p \leq 0.001$ compared to placebo groups). In general, 35% of LEV-treated patients were classified as responders, compared to 9.4% in the placebo groups ($p \leq 0.001$). The proportion of responders increased with the increase in dose; 28.6%, 35.2%, and 39.5% of patients responded at 1000, 2000, and 3000 mg/day of LEV, respectively (no statistical analyses were performed on these data). Shorvon and van Rijckevorsel (2002) reported that the percentage of patients experiencing a 75% or greater reduction in seizures was 11.8%, 16.8%, and 22.3% for patients receiving 1000, 2000, and 3000 mg/day of LEV, respectively, compared

with 3.3% in placebo-treated patients ($p \leq 0.001$ for all doses versus placebo). Of all patients treated with LEV, 5.7% became seizure-free, compared to 0.6% in the placebo group ($p \leq 0.001$) (Shorvon and van Rijkevorsel 2002). Leppik and colleagues made a separation between seizure types and showed that the median percentage of seizure reduction was 42.7% for simple partial seizures, 36.1% for complex partial seizures, and 68.5% for secondarily generalized seizures, respectively ($p \leq 0.05$ for all seizure types vs. placebo). The authors concluded that LEV seems to act at two levels: suppression of simple/complex partial seizures and prevention of secondary generalization (Leppik et al. 2003).

Several pooled analyses focusing on tolerability are available as well. Reviews by Harden, French, Arroyo, and their respective colleagues have pooled safety data from the well-controlled clinical trials discussed previously (Ben-Menachem and Falter 2000; Betts et al. 2000; Cereghino et al. 2000; Shorvon et al. 2000; French et al. 2001; Harden 2001; Arroyo and Crawford 2003). Adverse effects often limit the potential use of ACDs. During clinical trials with LEV, adverse effects were reported to be low, often not being significantly different from placebo, and easily resolved by dose reduction or discontinuation (Buck 2002; Welty et al. 2002). A summary of the most frequent adverse effects reported during the large clinical trials discussed in this review can be found in Table 1. In general, adverse events can be classified into three categories: somnolence/asthenia, coordination difficulties, and behavioral abnormalities/psychoses (Harden 2001). During the controlled trials, the most frequently reported side effects in LEV-treated patients were somnolence (14.8% vs. 8.4% in placebo), asthenia (14.7% vs. 9.1% in placebo), headache (13.7% vs. 13.4% in placebo), infection (13.4% vs. 7.5% in placebo), and dizziness (8.8% vs. 4.1% in placebo) (Harden 2001). These adverse events were seen most frequently in the first month of therapy and typically decreased or resolved with continued treatment (Harden 2001; Buck 2002; Welty et al. 2002). Coordination difficulties, including ataxia and abnormal gait, were present in 3.4% of LEV-treated patients compared to 1.6% in the respective placebo-treated group (Harden 2001; Arroyo and Crawford 2003). In the LEV groups, 13.3% of patients reported behavioral disorders including agitation, hostility, anxiety, apathy, emotional lability, depersonalization, depression, or other behavioral symptoms, compared to 6.2% in placebo-treated patients (Harden 2001). Few patients also displayed psychotic symptoms (0.7% compared to 0.2% in placebo) or suicidal behavior (0.5% compared to none in placebo) (Harden 2001). No clear relationship was noticeable between the dose of LEV used and the occurrence of the most frequent adverse events within the therapeutic dosage range of 1000–3000 mg/day (Harden 2001; Arroyo and Crawford 2003).

Although most reported adverse events were mild to moderate, 14.7% of LEV-treated patients and 11.2% of the placebo-treated groups experienced severe adverse events. Severe somnolence (3.1%), asthenia (1.6%), convulsions (1.6%), grand mal convulsions (1.0%), dizziness (0.7%), depression (0.7%), and personality disorders (0.5%) occurred more frequently in LEV-treated patients. Severe accidental injury (2.1%), headache (2.1%), status epilepticus (0.9%), pain (0.5%), confusion (0.5%), and insomnia (0.5%) had a higher prevalence in the placebo group (Harden 2001). In total, 15.0% of LEV-treated patients and 11.6% of placebo-treated patients either withdrew from their respective trial or required a dosage reduction (French et al. 2001; Harden 2001; Arroyo and Crawford 2003). Most common causes for withdrawal from the trial in the LEV group were somnolence (4.4% compared to 1.6% in placebo), convulsions (3% vs. 3.4% in placebo), dizziness (1.4% vs. 0% in placebo), asthenia (1.3% vs. 0.7% in placebo), and rash (none of the LEV group compared to 1.1% of placebo-treated patients) (French et al. 2001; Harden 2001; Arroyo and Crawford 2003).

When verifying for potential laboratory abnormalities and a possible influence of LEV on vital signs, statistically significant differences were found in LEV-treated patients compared to placebo (French et al. 2001; Harden 2001; Arroyo and Crawford 2003). Red blood cell count (mean change of $-0.05 \times 10^9/L$, $p = 0.035$), hemoglobin (mean change of -0.11 g/dL, $p = 0.010$), and hematocrit values (mean change of -0.37% , $p = 0.005$) were significantly lower in the LEV groups, but did not exceed standard laboratory normal ranges. White blood cell counts were slightly, but not significantly lower in the LEV group, and drug discontinuation due to neutropenia was not necessary in any of the patients. Results of various liver function tests were not different between patients taking LEV and the placebo group, and there was no evidence of LEV-induced changes in renal function or body weight. The adverse event profile was independent of gender (French et al. 2001; Harden 2001; Arroyo and Crawford 2003). Other than hypersensitivity to LEV or ingredients of the formulation, no contraindications for LEV have been formulated (Harden 2001).

The safety review by French and colleagues analyzed not only adverse event profiles of the controlled trials in epilepsy patients, but also those from several placebo-controlled studies of LEV in cognitive and anxiety disorders (French et al. 2001). Patients from the latter two populations were often on LEV monotherapy and in general received much lower doses than epilepsy patients (mean dose of 516 mg compared to 2421 mg in the epilepsy population). There were several interesting differences between the different populations. In epilepsy patients, infections (mainly respiratory and skin infections) were more common in the LEV-treated than in placebo groups, but this was not seen in the other populations. The authors hypothesized that the increase in infections in LEV-treated epilepsy patients was the result of an increase in social interactions due to seizure improvement. A higher incidence of behavioral problems was also reported in epilepsy patients taking LEV, but again not duplicated in any of the other two populations. This could suggest that epilepsy patients are more prone to experience behavioral disturbances than patients with cognitive or anxiety disorders, meaning that epilepsy patients with a history of behavioral problems treated with LEV should be carefully observed (French et al. 2001).

In conclusion, analysis of the regulatory trials provides strong evidence for the anti-convulsant effects of LEV add-on in adult patients with refractory partial epilepsy. LEV was shown to have a beneficial tolerability profile, a favorable responder ratio, and a low withdrawal rate, especially when compared indirectly with several other ACDs. LEV had a better responder rate than GPT and LTG, while equally well tolerated and a significantly lower withdrawal rate than TPM and OXZ with comparable efficacies (Otoul et al. 2005).

Long-term Results with LEV Add-on Therapy in Partial-Onset Seizures

In an attempt to clarify the long-term efficacy and retention rates for LEV add-on therapy, several reviews have pooled all original and follow-up data gathered during the clinical development program for LEV. This includes data from the four double-blind randomized multicenter controlled (regulatory-type) trials, five follow-up studies, and 26 phase II or open-label continuation trials, providing data from 1422 refractory patients with partial epilepsy who underwent LEV add-on therapy (intention-to-treat population) (Krakow et al. 2001; Ben-Menachem et al. 2003). The median daily dose of LEV was 3000 mg (Krakow et al. 2001; Ben-Menachem et al. 2003). LEV therapy showed a high continuation rate, sim-

ilar to or better than those reported for various other ACDs during development; 60% after one year, 37% after three years, and 32% after five years. Most withdrawals (43%) were due to problems intrinsic to ACD trials. Withdrawal due to adverse effects occurred in 15.8% of patients, with the most common causes being convulsions (3.4%)—inherent to a population of epilepsy patients, somnolence (2.0%), asthenia (0.6%), depression (0.6%), dizziness (0.5%), and headache (0.5%) (Krakow et al. 2001). The median reduction in seizure frequency over the whole treatment period was 39.6%, and responder rates determined after three months of LEV treatment were 39.2% (Krakow et al. 2001; Ben-Menachem et al. 2003). These numbers did not decrease significantly over time and no evidence for the development of tolerance was found. Again, no evidence was found for serious drug-related side effects or increased mortality (Krakow et al. 2001; Ben-Menachem et al. 2003).

Additional data on the long-term effects and retention rate of LEV are provided by several large-scale open-label trials. Patients in these community-based clinical settings are more diverse than patients in controlled clinical trials; they are more likely to have co-morbid medical conditions, to be older, to be receiving multiple ACDs, and to have less severe epilepsy than subjects enrolled in controlled trials (Morrel et al. 2003). The multicenter KEEPER¹ trial was a 16-week, phase IV open-label community-based trial that enlisted 1030 patients who responded inadequately to their current medications at the time (Morrel et al. 2003). LEV was added to their existing regimen at a maximum dose of 1000 mg/day (37.7%), 2000 mg/day (27.6%), or 3000 mg/day (29.8%). During the trial, the median reduction in partial seizure frequency was 62.3%, and 57.9% of patients showed at least 50% reduction in seizure frequency. A total of 72.5% of all patients originally included in the study (intention-to-treat [ITT] population) completed the entire study, with 12.9% of patients withdrawing due to adverse events, 2.8% due to lack of efficacy, and 11.8% due to other reasons. Adverse events were reportedly low and are summarized in Table 1. Serious adverse events, considered to be related to LEV treatment, occurred only in 0.3% of patients. Behavioral adverse events occurred at a low rate; hostility was noted in 1.7% of patients, emotional lability in 1.7%, depression in 1.5%, agitation in 1.2%, anxiety in 1.2%, and depersonalization in 0.1% of patients.

In an additional subgroup analyses of only elderly patients ($n = 78$) included in the KEEPER trial, 76.9% of patients were responders and an impressive number of 40.0% became seizure-free. As in the general population, LEV was well tolerated (Ferrendelli et al. 2003; Morrel et al. 2003).

The SKATE² study was another large, 16-week community-based phase IV multicenter trial that further evaluated the safety and efficacy of adjunctive LEV therapy in uncontrolled partial seizures in daily clinical practice (Genton et al. 2006). The study was completed in December 2005 and an interim analysis has recently been presented. Seven hundred and thirty-one patients were included in the analysis, showing a median reduction in seizure frequency of 47.8%, a responder rate of 48.4%, and a seizure-free rate of 16.8% at a median dose of LEV 2000 mg/day. Again, retention rates were high, with 84.4% of the ITT population completing the treatment period. Adverse events were not frequently reported and were mostly mild to moderate in nature (Table 1). Behavioral and psychiatric side effects were closely monitored and proved to be rare, including depression (3.4%), hostility (2.2%), emotional lability (1.1%), personality disorder (1.1%), anxiety (0.5%), and agitation

¹ Keppra Epilepsy Evaluation of the Patient time Response (KEEPER), conducted in the U.S.A.

² Safety of Keppra as Adjunctive Therapy in Epilepsy (SKATE), conducted in Europe.

(0.4%). Overall, 8.9% of patients experienced serious side effects. Adverse events led to withdrawal in 11.1% of patients, which was similar to the premarketing studies (10.3%) and the KEEPER trial (12.9%).

Results from the 16-week KEEPER and SKATE trials indicate that LEV is generally well tolerated in a patient population with refractory epilepsy as seen by epileptologists worldwide. Adverse events reported during long-term open-label studies have confirmed that chronic use of LEV does not appear to be associated with an increase in the incidence of adverse events or with the development of unexpected adverse effects (Arroyo and Crawford 2003; Bauer et al. 2006). In a long-term open label study of 505 patients receiving LEV (median dose: 3000 mg/day) with a mean follow-up of almost three years (range: 24 days to more than seven years), Bauer and colleagues reported adverse event profiles that were similar to those in short-term controlled trials, with the exception of somnolence, which was less prevalent in their trial (Bauer et al. 2006). The most commonly reported adverse effects during follow-up were convulsions (30.5%), accidental injury (28.1%), infection (21%), headache (20%), pain (13.9%), asthenia (12.9%), flu (11.3%), and dizziness (10.7%). In their population, the most common serious side effects were convulsions (9.5%) and accidental injuries (7.9%) and 7.7% of patients discontinued the study due to an adverse event. Bauer and colleagues confirmed the favorable tolerability profile of LEV at therapeutic doses in the treatment of refractory epilepsy, even when taken for several years (Bauer et al. 2006).

In conclusion, results from open label studies indicate that LEV is efficacious in a patient population with refractory epilepsy as seen by epileptologists worldwide and have also confirmed that LEV is generally well tolerated, with adverse events being mild to moderate in nature and serious adverse events being rare (Morrel et al. 2003; Genton et al. 2006). These studies seem to suggest a rule of thumb of roughly achieving a 50% reduction in seizure frequency in 50% of patients. This efficacy is higher than reported in the phase-III controlled studies, which could be explained by multiple reasons, mainly related to differences in study design and patient population (Morrel et al. 2003; Genton et al. 2006). In addition, long-term retention rates for LEV have proven to be high. In a large cohort of patients with chronic focal epilepsy, Depondt and colleagues reported an average retention rate (Kaplan–Meier survival analyses) in clinical practice of 58% at three years, suggesting LEV to be either more efficacious, better tolerated, or both, compared to LTG, TPM, and GPT (Depondt et al. 2006). Additionally, this report confirmed that almost half of patients involved in the study experienced a seizure reduction of at least 50%.

LEV Monotherapy in the Treatment of Partial-Onset Seizures

One of the regulatory trials discussed previously made the first switch into LEV monotherapy (Ben-Menachem and Falter 2000). Following the add-on phase of the trial, 69 responders were selected for down-titration of concomitant ACDs, with 71% being successfully converted to LEV monotherapy at 3000 mg/day and 52% completing the study. The median reduction in partial seizure frequency compared to baseline was 73.8% ($p = 0.037$), and the responder rate was 59.2%. Little more than 18% of patients remained seizure-free on LEV monotherapy. Ben-Menachem and Falter provided the first clear evidence that refractory patients responding to LEV add-on therapy could be successfully switched to LEV monotherapy. Since then, numerous case reports and small open-label studies have corrob-

orated these findings (e.g., Alsaadi and Thieman 2003; Alsaadi et al. 2005; Ben-Menachem 2003).

In a preliminary review on the long-term experience with LEV monotherapy, Ben-Menachem (2003) reported 67 patients who had been placed on LEV monotherapy for at least three months. Their seizure frequencies were low and remained stable over time. These patients had a high likelihood of becoming seizure-free; the probability of having a seizure-free period of almost three years was 52.2%. Little more than 73.5% of patients experienced one or more adverse events, but treatment-related serious adverse events were reported in only 4.1% of patients. Of the entire study population, 67.3% of patients on LEV monotherapy for at least three months completed the study (the duration of monotherapy in these patients ranged from 132 to 1968 days). Withdrawal due to adverse events occurred in 2% of patients, whereas 6.1% discontinued the drug due to loss or lack of efficacy. In general, LEV monotherapy proved to be well tolerated. The adverse events profile was consistent with that previously described in add-on therapy, but specific adverse effect ratios were not mentioned.

In April 2006, a first, well-controlled study was presented demonstrating the efficacy of LEV monotherapy in patients with partial or generalized seizures (Ben-Menachem et al. 2006). In this study, newly or recently diagnosed epilepsy patients ($n = 579$) were randomized to receive either LEV at a starting dose of 1000 mg/day or CBZ controlled release (CR) at a starting dose of 400 mg/day. This dose was maintained for a six-month evaluation period or until the next seizure. When a seizure occurred, doses were increased (LEV to 2000 mg/day or CBZ CR to 800 mg/day, and subsequently to LEV 3000 mg/day or to CBZ CR 1200 mg/day). Once six months of seizure freedom were achieved, patients entered a six-month maintenance period. In the ITT population, 66.7% of LEV- and 66.7% of CBZ CR-treated patients became seizure-free for at least six months. Of the 472 patients who adhered to the treatment protocol (per-protocol [PP] population), 56.6% of LEV and 58.5% of CBZ CR patients were seizure-free for one year. In addition, fewer patients on LEV (14.7%) than patients on CBZ CR (19.3%) required discontinuation of the treatment or change in the dose because of an adverse event. On the other hand, more patients discontinued the study because of lack of efficacy in the LEV group (17.5%) than in the CBZ CR group (10.0%). Overall, 80.8% of patients in the CBZ CR group and 79.6% of patients in the LEV group reported one or more adverse events (Table 1). Serious adverse events were seen in 10.0% of CBZ CR-treated patients and in 6.3% of the LEV-treated group. Overall, the safety profile appeared slightly more favorable in the LEV-treated patients, mainly because of the lower overall discontinuation rate. Neurological adverse events (depression, nervousness, and insomnia) were more prevalent in the LEV group than in the comparative CBZ CR group, whereas skin rash and gastrointestinal adverse effects were more prevalent in the CBZ CR group. Not unexpected, the tolerability profile of LEV in monotherapy was comparable to that in the adjunctive therapy in partial-onset seizures and again, the benefit-risk profile for LEV was highly favorable. Ben-Menachem and colleagues thus clearly demonstrated that LEV is noninferior to CR CBZ when used as monotherapy in the first-line treatment of adult patients with partial or generalized seizures. Although a margin of 15% (noninferiority) was selected, the adjusted absolute difference between the two treatments proved to be only 0.2%. As stated previously, these key results convinced the Committee for Medicinal Products for Human Use (CHMP) of EMEA to issue a positive opinion to approve marketing authorization for LEV as monotherapy in the treatment of partial-onset seizures with or without secondary generalization in patients from 16 years of

age with newly diagnosed epilepsy. The manufacturers plan to review these data with the FDA. To date, no superiority trials have been published, and approval for monotherapy has not yet been granted by the FDA. An elaborate conversion-to-monotherapy trial for partial seizures will start to enlist patients in the U.S.A. as of April 2007. The primary objective of this study³ is to assess the efficacy of LEV compared with a historical control as the placebo, in the monotherapy of patients with partial onset seizures.

LEV Add-on Therapy in Primary Generalized Epilepsy

In 2006, LEV was approved by both the EMEA and the FDA as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age suffering from JME. This approval came about following a key trial by Verdrú and colleagues (N166), extended with an open-label study (Verdrú et al. 2005). In their phase III double-blind randomized placebo-controlled study, the effect of LEV adjunctive therapy was assessed in patients ($n = 120$) suffering from primary generalized epilepsy with myoclonic seizures. Patients were randomized into a LEV 3000 mg/day or a placebo group, with both populations receiving only one concomitant ACD. Throughout the placebo-controlled trial, patients in the LEV group showed a mean reduction in myoclonic seizure-days/week of 48.5% and a responder rate of 58.3% compared to 8.9% and 23.3%, respectively, in the placebo group ($p = 0.0002$). A therapeutic benefit of LEV add-on therapy was already observed at a starting dose of 1000 mg/day. During the stable dosage period, 21.7% of LEV-treated patients became completely seizure-free compared to 3.4% in the placebo group ($p = 0.0001$).

During this placebo-controlled trial, 66.7% of placebo-treated patients and 75% of the LEV group experienced one or more adverse events, considered related to treatment in only half of the cases. In the LEV group, 3.2% of patients discontinued the therapy because of adverse events, compared to 1.7% in the placebo group. Of all patients exposed to LEV, 5% reported serious adverse events, while none occurred in the placebo group. In addition, nonpsychotic behavioral disorders (aggression, irritability, and staring), mood disorders (emotional lability, apathy, and depression), and sleep disorders occurred at least twice as often in the LEV group as in the placebo group (5.0%, 6.7%, and 6.7%, respectively, vs. 1.7%, 3.3%, and 1.7% in the placebo group). Nevertheless, LEV proved to be a safe and well-tolerated therapeutic option in this controlled trial; no new adverse effect findings were reported and the safety profile observed was comparable to that originally described in partial seizures. LEV thus proved to have a favorable benefit–risk profile in JME as well.

All of the patients included in this key trial were diagnosed with JME, but some also experienced primary generalized tonic–clonic seizures. Patients from this subgroup responded well to LEV therapy, with a median reduction of 84% in tonic–clonic seizure frequency, although this did not reach statistical significance due to the limited number of patients in this subpopulation ($p = 0.1228$). An even smaller subset of patients also presented themselves with absence seizures. LEV did not aggravate seizures—as is sometimes seen with several other ACDs effective in partial seizures—but also did not induce additional protection compared to placebo in this limited number of patients (Perucca 2001; Verdrú et al. 2005).

³ Official title: A Multi-Center, Double-Blind, Historical Control, Randomized Conversion to Monotherapy Study With Keppra XR for Treatment of Partial Onset Seizures.

Positive preliminary results of a phase III randomized, double blind, placebo-controlled trial have been recently presented (Rosenfeld et al. 2006). These investigators reported that during a 24-week trial, 72.2% of LEV-treated patients became responders, compared to 45.2% of placebo patients ($p = 0.0005$). During the stable dose period, 34.2% of LEV-treated and 10.7% of placebo-treated patients were free from primary generalized tonic-clonic seizures ($p = 0.001$). In addition, 24.1% of LEV-treated patients became completely seizure-free, compared to 8.3% in the placebo group ($p = 0.009$). Again, preliminary analysis suggested that LEV was safe and well tolerated in these patients. Safety data were similar to the established profile of LEV, the most commonly reported adverse effect being somnolence. During the double-blind period, 1.3% of LEV-treated patients and 4.8% of the placebo group withdrew due to adverse events. Further details on adverse events will be made available in the revised European Public Assessment Report (EPAR) after marketing authorization has been granted by the European Commission.

In response to this key trial, the CHMP of EMEA has issued a positive opinion recommending that the European Commission grant a marketing authorization for LEV as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and adolescents from 12 years of age with IGE.

Additionally, a large number of anecdotal case reports and small-scale open-label studies are available on adjunctive LEV-therapy in primary generalized epilepsy (Grünwald 2005). In summary, LEV add-on therapy appears to be safe and effective in primary generalized epilepsy, although further follow-up studies are necessary to confirm its long-term anticonvulsant profile.

LEV Monotherapy in Primary Generalized Epilepsy

Reports describing the effect of LEV monotherapy in primary generalized epilepsy are scarce and anecdotal at best. Hirsch and colleagues reported the effects of LEV monotherapy in six patients with refractory primary generalized epilepsy (Hirsch et al. 2002). Seizure control was adequate in these patients, especially in those with JME. LEV monotherapy was also assessed in a larger population of 24 patients with generalized tonic-clonic seizures and JME (Resor and Resor 2002). Myoclonic seizures were effectively controlled in 92% of patients, and approximately 67% of patients became free of tonic-clonic convulsions (Resor and Resor 2002). A study by Cohen demonstrated the beneficial effect of LEV monotherapy in another limited series of patients with refractory primary generalized epilepsy. These patients tolerated LEV at therapeutic doses well and became seizure-free for at least six months (Cohen 2003). A single-center open-label study in 21 patients reported that LEV monotherapy is effective, well tolerated, and safe in IGE and photosensitivity in children and adolescents (Covanis and Katsalouli 2003). Rocamora and colleagues reported that in several patients with primary generalized epilepsy, LEV monotherapy efficiently reduced ictal spike-waves (Rocamora et al. 2006). Finally, Labate and colleagues have shown that in patients with generalized epilepsy *de novo*, LEV monotherapy can effectively reduce myoclonic seizure frequency (Labate et al. 2006).

In conclusion, preliminary findings suggest that LEV adjunctive therapy and even monotherapy are likely to be effective in the treatment of primary generalized epilepsy as well as in the treatment of partial-onset seizures, but these findings need to be confirmed in more controlled studies. A pilot study of efficacy and tolerability of LEV monotherapy in subjects with childhood absence epilepsy (Cleveland Clinic, NIH clinical trials registry)

and a follow-up trial of LEV as monotherapy in patients with newly diagnosed epilepsy are currently recruiting patients.

LEV in a Pediatric Population

One well-controlled clinical trial has focused on the efficacy and safety of LEV in a pediatric population. Following promising results obtained in an open-label pediatric trial, Glauser and colleagues recently published the results of a multicenter, randomized, and placebo-controlled study in children ($n = 198$) with poorly controlled partial seizures (Glauser et al. 2002, 2006). The patients were randomized to receive either LEV 60 mg/kg/day or placebo. Over the entire treatment period, LEV-treated children experienced a median reduction in seizure frequency of 43.3% ($p \leq 0.0001$ vs. placebo) and showed a responder rate of 44.6% compared to 19.6% in the placebo group ($p = 0.0002$ vs. placebo). Again, LEV add-on therapy was well tolerated and proved to be highly effective (Glauser et al. 2006). One or more adverse events were experienced by 88.1% of the LEV-treated patients, compared to 91.8% in the placebo group. The most common adverse effects were somnolence (23% vs. 11% in placebo), accidental injury (17% vs. 10% in placebo), vomiting (15% vs. 13% in placebo), anorexia (13% vs. 8% in placebo), and rhinitis (13% vs. 8% in placebo). Some behavioral adverse events were reported, mostly hostility (11.9% compared to 6.2% in placebo), nervousness (9.9% vs. 2.1% in placebo), personality disorder (7.9% vs. 7.2% in placebo), emotional lability (5.9% vs. 4.1% in placebo), and agitation (5.9% vs. 1.0%). Discontinuation and dose reductions due to adverse events were more commonly reported in the placebo group than in LEV-treated patients, leading to withdrawal from the study in 9.3% of the placebo group and in 5.0% of LEV-treated patients. Serious adverse effects (not considered to be related to the drug) were reported in 7.9% of patients in the LEV-treated and in 9.3% of the placebo-treated patients. In general, adverse events were not statistically different between the placebo- and LEV-treated patients and the tolerability profile of LEV in children appeared to be similar to that previously reported for adults. This trial demonstrated that LEV is a safe and well-tolerated therapeutic option, even in a pediatric population. The manufacturers indicated, however, that the safety and effectiveness of LEV in children younger than four years of age has not been fully established (Keppra® package insert).

EMEA and FDA approval for LEV

LEV has been approved for monotherapy in partial-onset seizures in Europe, but not in the U.S.A. In Europe the EMEA recently approved the use of LEV as an adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with IGE. This indication is not yet approved by FDA. Several reasons can explain these differences.

Success with ACDs as add-on therapy is only the first step in the approval process for monotherapy. EMEA recommends noninferiority trials using established ACDs at optimized dosages as controls and demonstration of “no difference” or equivalence over the reference drug (usually within a 10% margin). These noninferiority monotherapy trials are considered by the EMEA as the best study design, even though supportive evidence from some kind of superiority trial is also recommended (Arroyo et al. 2004). The FDA does not accept

the validity of noninferiority trials and requires well-controlled trials, showing superiority of the test drug over control, usually placebo, as proof of efficacy. There has been a lot of debate concerning the ethics of using placebo in monotherapy trials, since these patients will obviously have a high risk of experiencing additional seizures. The use of placebo alone as a comparator is generally considered ethically unacceptable in epilepsy (Arroyo et al. 2004). Most superiority trials compare, therefore, a high dose of the test drug to suboptimal dosage of either the same drug or an established ACD (pseudoplacebo), making it hard to identify the optimal dose range of the test drug (Arroyo et al. 2004). Still, suboptimal treatment of patients involved in clinical trials is in conflict with the Declaration of Helsinki, one of the major international ethical guidelines for biomedical research involving human subjects, and more specifically with the principle of equipoise, which states that investigators are ethically obliged to offer the best therapeutic option to patients during a clinical trial (Freedman 1987). And last but certainly not least, once a given drug receives FDA approval for (adjunctive) epilepsy therapy, it is often used beyond the extensions granted by FDA approval as long as this would be beneficial for the patient (Bergey 2005). Therefore, new ACDs perceived as broad-spectrum drugs will frequently be used off-label as (initial) monotherapy or to treat patients with unapproved seizure types even before formal indications are granted (Bergey 2005).

POSTMARKETING SURVEILLANCE

Behavioral Adverse Events

Several additional tools for reporting adverse effects in a clinical setting (MEDWATCH, post-marketing antiepileptic drug survey database [PADS]) have provided safety data for LEV consistent with the known safety profile (Arroyo and Crawford 2003). Postmarketing surveillance has also revealed more details on a number of well-recognized neuropsychiatric adverse events possibly underestimated during clinical development. Mula and colleagues have published a report on 517 patients taking LEV (1000, 2000, or 3000 mg/day) and suffering from a diverse range of seizure types and epilepsy syndromes (partial epilepsy, generalized epilepsy, and Lennox-Gastaut) (Mula et al. 2003). Psychiatric adverse events were specifically monitored and occurred in 10.1% of patients: 3.5% displayed aggressive behavior, 2.5% an affective disorder, 2.5% depression, 2.3% emotional lability, 1.2% psychosis, 0.7% suicidal ideation, and 0.6% other behavioral abnormalities, such as anger, hostile behavior, and personality changes (Mula et al. 2003). Interestingly, Mula and colleagues found no significant correlation between the rate of psychiatric adverse events and starting dose of LEV or titration schedule. The authors suggested that clinical monitoring of these events is needed only in patients with increased biological vulnerability to developing psychiatric problems (Mula et al. 2003). In a separate study in 118 patients with epilepsy and learning disabilities, the same authors found that these patients were not more prone to develop psychiatric adverse events than the general population and that aggressive behavior was the main drug-related psychopathology (Mula et al. 2004). Several factors have already been suggested to facilitate the development of psychiatric adverse events during ACD therapy, including a history of psychopathology and previous occurrence of febrile seizures or status epilepticus (Mula et al. 2003, 2004).

White and colleagues published a case-controlled study incorporating a large number of patients ($n = 553$) from a prospective database and focused on behavioral side effects

(White et al. 2003). Almost 7% of their patients discontinued LEV because of behavioral side effects, and this proved to be the most common reason for withdrawal. The incidence of behavioral side effects was higher in this study than during premarketing studies, where the incidence of behavioral abnormalities leading to study withdrawal was 0.4% to 3.9% (Harden 2001; White et al. 2003). The authors concluded that, overall, LEV appears to be well tolerated, but could lead to worsening of behavioral symptoms in patients with an underlying predisposition. They identified a history of psychiatric problems, faster titration rate, and symptomatic generalized epilepsy as risk factors.

A recent study by Weintraub and colleagues compared psychiatric and behavioral side effects of the newer ACDs (Weintraub et al. 2006). In a population of 1394 adult patients, 16% of patients experienced psychiatric adverse events and significantly more of these events were linked to LEV therapy than to the other ACDs, even when controlling for a previous history of psychiatric issues ($p < 0.001$). Irritability (3.7%), depression (2.8%), and behavioral change (1.6%) were on average the most common psychiatric adverse events for all ACDs. Psychosis occurred in 1.6% of LEV-treated patients and, in general, patients taking LEV experienced significantly more irritability and a higher incidence of behavioral change compared to patients treated with the other drugs ($p < 0.001$). Nevertheless, the authors explicitly state that, despite this, the majority of patients who were treated with LEV did not experience psychiatric adverse events at all, and LEV remained one of the most effective new ACDs in their patient population as measured by 12-month retention rates (Weintraub et al. 2006). Following reports of adverse psychiatric effects, the manufacturers issued, however, a warning for the use of LEV in patients who may be predisposed to psychiatric disorders (Keppra[®] package insert).

Pregnancy

Women taking ACDs who want to become pregnant are challenged with several obstacles. There were no indications from preclinical studies that LEV adversely affects fertility, although recent findings seem to suggest at least some influence on reproductive hormones (French 2001; Taubøll et al. 2006). Fertility problems, often as the result of reproductive endocrine dysfunction induced by epilepsy, ACD intake, or both, have been reported in women with epilepsy. VPA for instance has been associated with development of polycystic ovaries, menstrual disorders, and hyperandrogenism (Taubøll et al. 2006). Short-term VPA treatment can disrupt follicular steroidogenesis (resulting in increased testosterone and decreased estradiol secretion) and may act as an apoptotic agent in both small- and medium-sized follicles (Taubøll et al. 2002, 2003). A recent study by Taubøll and colleagues established that both VPA and LEV affect endocrine function in prepubertal porcine ovarian follicular cells and argues that LEV might have an effect on reproductive function only in women with low gonadotropin levels, whereas VPA seems to affect endocrine function independent of gonadotropin levels (Taubøll et al. 2006).

At least two large databases exist which incorporate pregnant women taking ACDs: the North American Antiepileptic Drug Pregnancy Registry⁴ and the European International Registry of Antiepileptic Drugs and Pregnancy⁵ (EURAP). UCB, Inc. has also established the KEPPRA Pregnancy Registry⁶ to monitor safety and outcomes associated with pregnant

⁴ Enrolling is possible for healthcare providers and patients by calling (888) 233-2334.

⁵ Contact data per country are available at <http://www.eurapinternational.org/>

⁶ Enrolling is possible for healthcare providers and patients by calling (888) 537-7734.

women being treated with LEV. These databases should advance our understanding of the safety issues associated with ACD intake and pregnancy. To date, there are few or no adequate controlled studies and the only clear indications on the effect of LEV in pregnancy come from laboratory animals, showing potential adverse effects on the fetus mainly at supratherapeutic doses. Not surprisingly, LEV is regarded as Pregnancy Category C, meaning that potential benefits may warrant use of the drug in pregnant women despite potential risks.

During well-controlled trials in the development of LEV, 23 women became pregnant while taking LEV 1000–4000 mg/day as either monotherapy or adjunctive therapy (French et al. 2001; ten Berg et al. 2005). Pregnancy outcomes were: eight healthy children, one child with syndactyly, one child with congenital heart disease, one prematurely delivered child with abnormal heart rhythm, one ectopic pregnancy, seven spontaneous and three voluntary abortions, and two unknown outcomes. No data were published on the birth weights. One series of case reports has shown a normal pregnancy outcome and regular birth weights in three patients on LEV monotherapy at a dose of 750–3000 mg LEV daily (Long 2003). Ten Berg and colleagues presented the outcome of 11 well-documented pregnancies from a consecutive series of LEV-exposed pregnancies registered in EURAP in The Netherlands (ten Berg et al. 2005). LEV was prescribed as monotherapy to two women and as combination therapy to eight women (doses varied from 500 to 3500 mg/day). Nine pregnancies resulted in the birth of a child and two pregnancies ended in abortion (one spontaneous, one voluntary). No fetal malformations were detected, but two of nine live-born children had a low birth weight (<10th centile) and one had a very low birth weight (<2.3rd centile). This could be related to LEV intake. The authors could not establish a clear effect on birth weight but suggested a possible association (ten Berg et al. 2005; ten Berg et al. 2006). Because low birth weight is associated with increased morbidity and mortality, these findings certainly warrant further investigation (ten Berg et al. 2005).

Recently, preliminary data for the use of LEV in pregnancy were reported from the UK Epilepsy and Pregnancy Register (UKEPR) (Hunt et al. 2006). The UKEPR is a prospective pregnancy register set up to determine the relative safety of all ACDs taken during pregnancy. The authors identified 117 women who had become pregnant and were taking LEV, either as monotherapy ($n = 39$) or in combination with other ACDs ($n = 78$). In total, 93% of pregnancies resulted in successful birth. Abnormalities were noted in 7.3% of pregnancies, of which 2.7% were major congenital malformations (pyloric stenosis in one and spina bifida in two patients) that all occurred in patients on combination therapy with other ACDs. Low birth weight occurred in 11.4% of infants exposed to monotherapy and in 12.9% of infants exposed to combination therapy. Minor congenital malformations were observed in 4.3% of infants, all of whom were again exposed to adjunctive LEV therapy. These results were well within the range reported for all other ACDs. The authors mentioned that a larger number of patients needs to be studied before conclusive evidence on the effect of LEV in pregnancy can be presented (Hunt et al. 2006).

Johannessen et al. (2005) measured LEV concentrations in serum and in breast milk at birth and during lactation. The findings suggested extensive transfer of LEV from mother to fetus (LEV readily crosses the placenta) and into breast milk (mean milk/maternal serum concentration equaled 1). Breast-fed infants usually had very low LEV serum concentrations, suggesting rapid elimination of LEV or reduced absorption. The authors indicated that no malformations or adverse events were detected, and in general would encourage women to breastfeed their infants, even when taking LEV.

CONCLUSIONS

In a clinical setting, LEV has proven to be a well tolerated and efficacious ACD against a broad range of seizure types. Long-term retention rates for LEV are high and no proof for the development of tolerance has been reported. In addition, LEV therapy is accompanied by a high percentage of responders and a low “number needed to treat” (mean number of patients needed to be treated to obtain one extra responder over placebo) (van Rijckevorsel and Boon 2001). LEV’s pharmacokinetic characteristics are highly desirable, and according to some even closely resemble those of an ideal ACD, limiting the need for therapeutic drug monitoring (Patsalos 2000, 2004). In conclusion, LEV is a safe and unique addition to ACDs used in clinical practice.

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REFERENCES

- Alsaadi TM, Thieman C (2003) Levetiracetam monotherapy for newly diagnosed epilepsy patients. *Seizure* 12:154-156.
- Alsaadi TM, Shatzel A, Marquez AV, Jorgensen J, Farias S (2005) Clinical experience of levetiracetam monotherapy for adults with epilepsy: 1-year follow-up study. *Seizure* 14:139-142.
- Arroyo S, Crawford P (2003) Safety profile of levetiracetam. *Epileptic Disord* 5:57-63.
- Arroyo S, Chadwick DW, French J, Mattson R, Perucca E (2004) Epilepsies and convulsive disorders, Chapter 16, in: *The IUPHAR Compendium of Basic Principles For Pharmacological Research in Humans* (du Souich P, Orme M, Erill S eds.) p. 165-182, International Union of Basic and Clinical Pharmacology, Irvine, California.
- Bauer J, Ben-Menachem E, Kramer G, Fryze W, Da Silva S, Kasteleijn-Nolst TDG (2006) Levetiracetam: A long-term follow-up study of efficacy and safety. *Acta Neurol Scand* 114:169-176.
- Ben-Menachem E (2003) Preliminary efficacy of levetiracetam in monotherapy. *Epileptic Disord* 5:51-55.
- Ben-Menachem E, Falter U (2000) Efficacy and tolerability of levetiracetam 3000 mg in patients with refractory partial seizures: A multicenter, double-blind, responder-selected study evaluating monotherapy. *Epilepsia* 41:1276-1283.
- Ben-Menachem E, Edrich P, Van Vleymen B, Sander JW, Schmidt B (2003) Evidence for sustained efficacy of levetiracetam as add-on epilepsy therapy. *Epilepsy Res* 53:57-64.
- Ben-Menachem E, Brodie MJ and Perucca E on behalf of the N01061 Study Group (2006) Efficacy of levetiracetam monotherapy; randomized double-blind head-to-head comparison with carbamazepine-CR in newly diagnosed epilepsy patients with partial onset or generalized tonic-clonic seizures. Presented at the American Academy of Neurology, April 2006 and discussed in EMEA procedure number EMEA/H/C/277/II/63.
- Bergey GK (2005) Evidence-based treatment of idiopathic generalized epilepsies with new antiepileptic drugs. *Epilepsia* 46:161-168.
- Betts T, Waegemans T, Crawford P (2000) A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. *Seizure* 9:80-87.

- Boon P, Chauvel P, Pohlmann-Eden B, Otoul C, Wroe S (2002) Dose-response effect of levetiracetam 1000 and 2000 mg/day in partial epilepsy. *Epilepsy Res* 48:77-89.
- Buck ML (2002) Levetiracetam for the treatment of partial seizures. *Pediatric Pharmacoth* 8:1-5.
- Cereghino JJ, Biton V, Abou-Khalil B, Dreifuss F, Gauer LJ, Leppik I (2000) Levetiracetam for partial seizures: Results of a double-blind, randomized clinical trial. *Neurology* 55:236-242.
- Cohen J (2003) Levetiracetam monotherapy for primary generalized epilepsy. *Seizure* 12:150-153.
- Covanis A, Katsalouli M (2003) Levetiracetam monotherapy in generalized epilepsy and photosensitivity. *Epilepsia* 44:80 [abstract].
- Depondt C, Yuen AWC, Bell GS, Mitchell T, Koepp MJ, Duncan JS, Sander JW (2006) The long-term retention of levetiracetam in a large cohort of patients with epilepsy. *JNNP* 77:101-103.
- Edwards KR, Glantz MJ, Bator T, Button J (2004) Levetiracetam levels in human cerebrospinal fluid: A controlled, dose ranging pharmacokinetic study. *Neurology* 62:118 [abstract].
- Ferrendelli JA, French J, Leppik I, Morrell MJ, Herbeuval A, Han J, Magnus L (2003) Use of levetiracetam in a population of patients aged 65 years and older: A subset analysis of the KEEPER trial. *Epilepsy Behav* 4:702-709.
- Freedman B (1987) Equipoise and the ethics of clinical research. *N Engl J Med* 317:141-145.
- French J (2001) Use of levetiracetam in special populations. *Epilepsia* 42:40-43.
- French J, Edrich P, Cramer JA (2001) A systematic review of the safety profile of levetiracetam: A new antiepileptic drug. *Epilepsy Res* 47:1-2.
- Genton P, Sadzot B, Fejerman N, Peltola J, Despland PA, Steinhoff B, Rektor I, Wroe S, Maubrey MC, Vandervelden C, et al. (2006) Levetiracetam in a broad population of patients with refractory epilepsy: Interim results of the international SKATE trial. *Acta Neurol Scand* 113:387-394.
- Glauser TA, Pellock JM, Bebin EM, Fountain NB, Ritter FJ, Jensen CM, Shields WD (2002) Efficacy and safety of levetiracetam in children with partial seizures: An open-label trial. *Epilepsia* 43:518-524.
- Glauser TA, Ayala R, Elterman RD, Mitchell WG, Van Orman CB, Gauer LJ, Lu Z; N159 Study Group (2006) Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. *Neurology* 66:1654-1660.
- Grant R, Shorvon SD (2000) Efficacy and tolerability of 1000–4000 mg per day of levetiracetam as add-on therapy in patients with refractory epilepsy. *Epilepsy Res* (42):89-95.
- Grünewald R (2005) Levetiracetam in the treatment of idiopathic generalized epilepsies. *Epilepsia* 46:154-160.
- Harden CL (2001) Safety profile of levetiracetam. *Epilepsia* 42:36-49.
- Harden CL, Leppik I (2006) Optimizing therapy of seizures in women who use oral contraceptives. *Neurology* 67:S56-S58.
- Hirsch E, Thibault-Menard A, Valenti MP, Chassagnon S (2002) Open study on the efficacy of levetiracetam monotherapy in idiopathic generalized epilepsies. *Epilepsia* 43:62 [abstract].
- Hunt S, Craig J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, Irwin B, Morrison PJ, Morrow J. (2006) Levetiracetam in pregnancy: Preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 67:1876-1879.
- Johannessen SI, Helde G, Brodtkorb E (2005) Levetiracetam concentrations in serum and in breast milk at birth and during lactation. *Epilepsia* 46:775-777.
- Kasteleijn-Nolst TDGA, Marescaux C, Stodieck S, Edelbroek PB, Oosting J (1996) Photosensitive epilepsy: A model to study the effects of antiepileptic drugs: Evaluation of the piracetam analogue, levetiracetam. *Epilepsy Res* 25:225-230.
- Kelly K, Stephen LJ, Brodie MJ (2004) Levetiracetam for people with mental retardation and refractory epilepsy. *Epilepsy Behav* 5: 878-883.
- Krakow K, Walker M, Otoul C, Sander JW (2001) Long-term continuation of levetiracetam in patients with refractory epilepsy. *Neurology* 56:1772-1774.
- Labate A, Colosimo E, Gambardella A, Leggio U, Ambrosio R, Quattrone A (2006) Levetiracetam in patients with generalised epilepsy and myoclonic seizures: An open label study. *Seizure* 15:214-218.
- Leppik IE, Biton V, Sander JW, Wieser HG (2003) Levetiracetam and partial seizure subtypes: Pooled data from three randomized, placebo-controlled trials. *Epilepsia* 44:1585-1587.
- Long L (2003) Levetiracetam monotherapy during pregnancy: A case series. *Epilepsy Behav* 4:447-448.
- May TW, Rambeck B, Jurgens U (2003) Serum concentrations of levetiracetam in epileptic patients: The influence of dose and co-medication. *Ther Drug Monit* 25:690-699.
- McAuley JW, Anderson GD (2002) Treatment of epilepsy in women of reproductive age: Pharmacokinetic considerations. *Clin Pharmacokinet* 41:559-579.

- Meencke HJ, Buyle S (2006) Assessment of a dose-response relationship of levetiracetam. *Eur J Neurol* 13:942-946.
- Morrell MJ, Leppik I, French J, Ferrendelli J, Han J, Magnus L (2003) The KEEPER trial: Levetiracetam adjunctive treatment of partial-onset seizures in an open-label community-based study. *Epilepsy Res* 54:153-161.
- Mula M, Trimble MR, Yuen A, Liu RS, Sander JWAS (2003) Psychiatric adverse events during levetiracetam therapy. *Neurology* 61:704-706.
- Mula M, Trimble MR, Sander JWAS (2004) Psychiatric adverse events in patients with epilepsy and learning disabilities taking levetiracetam. *Seizure* 13:55-57.
- Otoul C, Arrigo C, van Rijckevorsel KJ, French JA (2005) Meta-analysis and indirect comparisons of levetiracetam with other second-generation antiepileptic drugs in partial epilepsy. *Clin Neuropharmacol* 28:72-78.
- Patsalos PN. (2000) Pharmacokinetic profile of levetiracetam: Toward ideal characteristics. *Pharmacol Ther* 85:77-85.
- Patsalos PN (2004) Clinical pharmacokinetics of levetiracetam. *Clin Pharmacokinet* 43:707-724.
- Pellock JM, Glauser TA, Bebin EM, Fountain NB, Ritter FJ, Coupez RM, Shields WD (2001) Pharmacokinetic study of levetiracetam in children. *Epilepsia* 42:1574-1579.
- Perucca E, Baltes E, Ledent E (2000) Levetiracetam: Absence of pharmacokinetic interactions with other antiepileptic drugs (AEDs). *Epilepsia* 41:150 [abstract].
- Perucca E (2001) The management of refractory idiopathic epilepsies. *Epilepsia* 42:31-35.
- Perucca E, Gidal BE, Baltes E (2003) Effects of antiepileptic comedication on levetiracetam pharmacokinetics: A pooled analysis of data from randomized adjunctive therapy trials. *Epilepsy Res* 53:47-56.
- Privitera M (2001) Efficacy of levetiracetam: A review of three pivotal clinical trials. *Epilepsia* 42:31-35.
- Ramael S, Daoust A, Otoul C, Toubiane N, Troenaru M, Lu ZS, Stockis A (2006a) Levetiracetam intravenous infusion: A randomized, placebo-controlled safety, and pharmacokinetic study. *Epilepsia* 47:1128-1135.
- Ramael S, De Smedt F, Toubiane N, Otoul C, Boulanger P, Riethuisen JM, Stockis A (2006b) Single-dose bioavailability of levetiracetam intravenous infusion relative to oral tablets and multiple-dose pharmacokinetics and tolerability of levetiracetam intravenous infusion compared with placebo in healthy subjects. *Clin Ther* 28:734-744.
- Ragueneau-Majlessi I, Levy RH, Janik F (2002) Levetiracetam does not alter the pharmacokinetics of an oral contraceptive in healthy women. *Epilepsia* 43:697-702.
- Resor SR, Resor LD (2002) Levetiracetam monotherapy in the treatment of convulsive seizures in juvenile myoclonic epilepsy. Presented at the 54th Annual Meeting of the American Academy of Neurology In: Grünwald R (2005) Levetiracetam in the treatment of idiopathic generalized epilepsies. *Epilepsia* 46:154-160.
- Rocamora R, Wagner K, Schulze-Bonhage A (2006) Levetiracetam reduces frequency and duration of epileptic activity in patients with refractory primary generalized epilepsy. *Seizure* 15:428-433.
- Rosenfeld WE, Berkovic S and Knowlton R on behalf of LEV N01057 PGTC Study Group (2006) Efficacy and safety of levetiracetam as adjunctive treatment in adult and pediatric subjects suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic seizures. *Neurology* 66:A40 [abstract].
- Shorvon SD, Lowenthal A, Janz D, Bielen E, Loiseau P for the European Levetiracetam Study Group (2000) Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. *Epilepsia* 41:1179-1186.
- Shorvon SD, van Rijckevorsel KJ (2002) A new antiepileptic drug. *JNNP* 72:426-429.
- Sisodiya SM, Sander JW, Patsalos PN (2002) Carbamazepine toxicity during combination therapy with levetiracetam: A pharmacodynamic interaction. *Epilepsy Res* 48:217-219.
- Sohn YH, Kaelin-Lang A, Jung HY, Hallett M (2001) Effect of levetiracetam on human corticospinal excitability. *Neurology* 57:858-863.
- Taubøll E, Wójtowicz AK, Ropstad E, Gregoraszcuk EL (2002) Valproate irreversibly alters steroid secretion patterns from porcine follicular cells in vitro. *Reprod Toxicol* 16:319-325.
- Taubøll E, Gregoraszcuk EL, Kolodziej A, Kajta M, Ropstad E (2003) Valproate inhibits the conversion of testosterone to estradiol and acts as an apoptotic agent in growing porcine ovarian follicular cells. *Epilepsia* 44:1014-1021.
- Taubøll E, Gregoraszcuk EL, Tworzydo A, Wójtowicz AK, Ropstad E (2006) Comparison of reproductive effects of levetiracetam and valproate studied in prepubertal porcine ovarian follicular cells. *Epilepsia* 47:1580-1583.

- ten Berg K, Samren EB, van Oppen AC, Engelsman M, Lindhout D (2005) Levetiracetam use and pregnancy outcome. *Reprod Toxicol* 20:175-178.
- ten Berg K, van Oppen ACC, van Donselaar CA, Wentges-van Holthe JM, Koppe WM, Tamminga P, Lindhout D (2006) Outcomes of human pregnancies after levetiracetam exposure. *Birth Defects Res Part A Clin Mol Teratol* 76:318.
- van Rijckevorsel K, Boon P (2001) The number needed to treat with levetiracetam (LEV): Comparison with the other new antiepileptic drugs (AEDs). *Seizure* 10:235-236.
- Verdrü P, Wajgt A, Schiemann Delgado J, Noachtar S (2005) Efficacy and safety of levetiracetam 3000 mg/d as adjunctive treatment in adolescents and adults suffering from idiopathic generalized epilepsy with myoclonic seizures. *Epilepsia* 46:56 [abstract]; discussed fully in EMEA guideline EMEA/H/C/277/II/61.
- Weintraub D, Buchsbaum R, Resor SR Jr, Hirsch LJ (2006) Psychiatric and behavioral side effects of the newer antiepileptic drugs in adults with epilepsy. *Epilepsy Behav* Oct 30 [Epub ahead of print].
- Welty TE, Gidal BE, Ficker DM, Privitera MD (2002) Levetiracetam: A different approach to the pharmacotherapy of epilepsy. *Ann Pharmacother* 36:296-304.
- White JR, Walczak TS, Leppik IE, Rarick J, Tran T, Beniak TE, Matchinsky DJ, Gumnit RJ (2003) Discontinuation of levetiracetam because of behavioral side effects: A case-control study. *Neurology* 61:1218-1221.