8.7.5.3 All Adult Epilepsy Patients

Among 1166 patients with urinalysis results the mean urinary pH was 6.3 At analysis visit 6 months to 1 year mean urinary pH value was 6.1.

8.8 Vital signs

The sponsor discusses the methods used to evaluate laboratory data on page 46 of the SU. Vital signs measurements are primarily available from the controlled epilepsy studies. Measurements were summarized at the baseline visit and at each analysis visit window. If measurements were taken in various postures only the supine measurement was recorded, or the standing measurement if no supine measurement was recorded. When multiple measurements were available within a visit window the "worst" value was chosen. The following criteria were applied to identify possibly clinically significant abnormalities in vital signs:

Pulse rate	$\leq$ 50 bpm and a decrease of $\geq$ 30 bpm $\geq$ 120 bpm and an increase of $\geq$ 30 bpm
Systolic BP	$\leq$ 90 mmHg and a decrease of $\geq$ 30 mmHg $\geq$ 180 mmHg and an increase of $\geq$ 40 mmHg
Diastolic BP	$\leq$ 50 mmHg and a decrease of $\geq$ 20 mmHg $\geq$ 105 mmHg and an increase of $\geq$ 30 mmHg
Weight	change of $\geq$ 7% of baseline weight

Additional measurements are available from the adult epilepsy studies through November 30, 1998 and from the patients participating in trials of other indications.

8.8.1 Controlled Trials: Mean Change from Baseline Analysis

The following table summarizes the results of the mean change from baseline analysis for vital signs measurements in controlled epilepsy studies. Mean changes from baseline were generally small and did not appear to be of clinical significance.

Table 71: Summary of Mean Change from Baseline to Final Visit by Treatment Group: Vital Signs Measurements in Adequate and Well-Controlled Studies (both periods of Study N051)

Measurement (unit)	Levetiracetam mean change from baseline (n)	Placebo mean change from baseline (n)
Systolic BP (mmHg)	-1.65 (754)	-0.93 (434)
Diastolic BP (mmHg)	-1.04 (754)	0.00 (434)
Pulse (bpm)	-0.13 (753)	0.42 (434)
Body Weight (kg)	0.04 (756)	0.27 (433)

based on sponsor's Tables 120A,130A, and 137A, SU

8.8.1.1 Blood Pressure

With respect to systolic blood pressure 6 (0.8%) levetiracetam and 3 (0.7%) placebo-treated patients met the criteria of a PCS low systolic blood pressure. For diastolic blood pressure 4 (0.5%) levetiracetam and 1(0.2%) placebo-treated patients met the criteria of a PCS low diastolic blood pressure. On my review of sponsor's Table 121A, the lowest recorded systolic blood pressure was 84 mmHg, and the lowest diastolic blood pressure was 50 mmHg. A PCS increase in systolic blood pressure was noted for 5 (0.7%) of levetiracetam and 3 (0.7%) of placebo-treated patients

Three (0.4%) of levetiracetam and 4 (0.9%) of placebo-treated patients had a treatment-emergent adverse event of hypotension that did not meet PCS criteria. None of the events were considered serious adverse

events. Seven (0.9%) of levetiracetam and 2 (0.5%) of placebo-treated patients had a treatment-emergent adverse event of hypertension that did not meet PCS criteria.

When all adult epilepsy studies were examined, a total of 23 (1.7%) patients met the criteria of a low PCS systolic blood pressure and 22 (1.6%) patients met the criteria of a low PCS diastolic blood pressure. A total of 19 (1.4%) patients met the criteria of an elevated PCS systolic blood pressure and 20 (1.5%) patients met the criteria of an elevated PCS diastolic blood pressure.

8.8.1.2 Pulse

With respect to pulse 1 (0.1%) levetiracetam and none of the placebo-treated patients met the criteria of a PCS low pulse. A PCS increase in pulse was noted for 1 (0.1%) of levetiracetam and 1 (0.2%) of placebo-treated patients.

Three (0.4%) of levetiracetam and 2 (0.5%) of placebo-treated patients had a treatment-emergent adverse event of tachycardia that did not meet PCS criteria. None of the events were considered serious adverse events. One (0.1%) of levetiracetam and 1 (0.2%) of placebo-treated patients had a treatment-emergent adverse event of bradycardia that did not meet PCS criteria. None of the events were considered serious adverse events.

When all adult epilepsy studies were examined, a total of 7 (0.5%) of levetiracetam-treated patients met the criteria of a low PCS pulse and 4 (0.3%) of levetiracetam-treated patients met the criteria of a elevated PCS pulse.

When all adult epilepsy studies were examined 3 levetiracetam-treated patients (1 patient from the controlled studies) were reported with the event bradycardia. None of the pulse measurements met the criteria for possible clinical significance. Twelve levetiracetam-treated patients experienced sinus bradycardia. None of the pulse measurements met the criteria for possible clinical significance. None were reported as a serious adverse event.

8.8.1.3 Body Weight

With respect to weight 47 (6.2%) levetiracetam and 22 (5.0%) of the placebo-treated patients met the criteria of a PCS increase in weight. A PCS decrease in weight was noted for 41(5.4%) of levetiracetam and 17 (3.9%) of placebo-treated patients.

8.9 Electrocardiogram (ECG) Data

ECG data was analyzed by four methods:

- patients with epilepsy were analyzed for whether or not the worst on treatment ECG was interpreted as abnormal or not, and the proportion of patients with treatment emergent abnormalities tallied;
- adverse events indicative of ECG abnormalities for patients with epilepsy and other indications were reviewed;
- baseline and end of evaluation ECG tracings from studies N051, N132 and N138 were re-read and had intervals calculated and abnormalities identified which were then reviewed by a single cardiologist;
- ECG tracings from studies N043, N044 and N045 (placebo-controlled trials in general anxiety disorders) were evaluated.

8.9.1 Adult Patients with Epilepsy: Worst On-Treatment ECG Analysis

There were 1061 levetiracetam and 224 placebo-treated adult epilepsy patients with baseline and on-treatment ECGs. Among patients with a normal ECG at baseline, 88 (8.3%) of levetiracetam and 11 (4.9%) of placebo-treated patients developed a treatment-emergent abnormality.

8.9.2 Controlled Trials of Epilepsy: ECG-Related Adverse Events

The sponsor reviewed treatment-emergent adverse events reflective of ECG changes and the events identified are summarized in Table 72. Patient **2464** had an adverse event of heart block. The sponsor

reports that this patient had left anterior hemiblock occurring after 1 day of treatment with levetiracetam 1000 mg/day. The event is described as mild and present 1 year later. There did not appear to be any notable differences between the levetiracetam and placebo-treated patients for ECG related treatment-emergent adverse events.

Table 72: ECG Related Adverse Events, Controlled Trials of Epilepsy

Preferred Term	Levetiracetam (N = 769)	Placebo (N = 439)
Bradycardia	1 (0.1%)	1 (0.2%)
Tachycardia	3 (0.4%)	2 (0.5%)
Heart block	1 (0.1%)	0
Bundle branch block	2 (0.3%)	2 (0.6%)
Myocardial ischemia	1 (0.1%)	0
Electrocardiogram abnormal	6 (0.8%)	4 (1.1%)
Ventricular extrasystoles	0	1 (0.2%)
Sinus bradycardia	0	1 (0.2%)

8.9.3 Controlled Trials of Epilepsy: ECG Analysis

ECG data from the controlled trials of epilepsy were analyzed by four methods. Mean change from baseline was calculated for each treatment group (End of Evaluation - Baseline). Shift analyses were generated using the following criteria: heart rate < 60 or > 120, PR ≥ 200msec, QRS ≥ 100 msec, and QTc ≥ 440 msec. Possibly clinically significant percent changes from baseline were generated using the following criteria: heart rate decrease ≤ 20% or increase ≥19%, PR and QRS increase ≥ 25%, and QTc increase ≥ 15%. Treatment-emergent ECG abnormalities included changes in conduction, hypertrophy, myocardial infarction, ST, T waves, and/or U waves and new arrhythmias present at end of evaluation and not present on baseline ECG.

For the ECG data from the three controlled studies in epilepsy there did not appear to be any notable changes from baseline for QRS, PR, or QTc when comparing the levetiacetam and placebo groups (Table 73).

With respect to heart rate there was a decrease from baseline in levetiracetam-treated patients of –1.1 bpm compared to a decrease from baseline in placebo-treated patients of –0.8 bpm. For Study N138, where patients received levetiracetam at a dose of 3000 mg/day, the difference between levetiracetam and placebo was more marked [difference in mean changes (levetiracetam – placebo) = -2.7 bpm]. However, the difference in mean changes for the Study N132 3000 mg/day group – placebo group was only 0.1 bpm, suggesting an inconsistent effect by dose.

When examining heart rate by shift analyses 65.8% of levetiracetam, and 73.8% of placebo-treated patients were normal at baseline and at the end of evaluation. Among the patients normal at baseline and not at the end of evaluation the largest difference between levetiracetam and placebo (5.8% difference) was for those patients normal at baseline but had bradycardia (heart rate <60 bpm) at the end of evaluation. The sponsor examined the levetiracetam - placebo difference for this sequence to further explore the relationship by study and dose. For Studies N051 and N132 the levetiracetam -placebo difference was 4.6% and 3.4%, respectively. For Study N138 (levetiracetam-treated patients received 3000 mg/day) the levetiracetam-placebo difference was 10%. However, the levetiracetam 3000 mg/day - placebo difference for Study N132 was 4.1% suggesting an inconsistent effect by dose. When examining the inverse shift, bradycardia to normal, more levetiracetam-treated patients were normal at the end of evaluation than placebo-treated patients (levetiracetam - placebo = 1.6%).

The sponsor examined shifts using a lower cut point for bradycardia of less than or equal to 50 bpm. There were 13 (2.2%) levetiracetam and 1 (0.3%) placebo-treated patients who were within normal limits at baseline and who had bradycardia at end evaluation. When examining the inverse shift (bradycardia to

normal) more levetiracetam-treated patients 15 (2.5%) were normal at the end of evaluation than placebo-treated patients 3 (1%).

In the percent change from baseline analysis more placebo-treated patients showed a clinically significant decline in heart rate (8.3%) as compared to levetiracetam-treated patients (7.6%). However, it must be kept in mind that the criteria used for the percent change analysis (≤ 20% decrease in heart rate) does not necessarily mean that a patient developed possibly clinically significant bradycardia.

Table 73: ECG Interval Evaluation in Controlled Studies of Epilepsy (N051, N132, and N138)

Interval (units)	Levetiracetam n = 596	Placebo n = 301
PR Interval (msec)		
Mean change from baseline	1.0	0.2
Shift analysis (WNL – WNL)	97.3%	96.3%
Percent change from baseline[a]	0.7%	1.7%
QRS Interval (msec)		
Mean change from baseline	0.5	0.7
Shift analysis (WNL – WNL)	92.4%	89.7%
Percent change from baseline	0	1.3%
QTc Interval (msec)		
Mean change from baseline	-1.5	-2.7
Shift analysis (WNL – WNL)	96.8%	97.3%
Percent change from baseline	0.5%	0.3%
Rate (bpm)		
Mean change from baseline	-1.1	-0.8
Shift analysis (WNL – WNL)	65.8%	73.8%
Percent change from baseline	16.8%	19.3%

[a]Percent of patients with a possibly clinically significant change from baseline

A single cardiologist identified treatment-emergent abnormalities. The only abnormality with an occurrence of greater than 2% was sinus bradycardia (2.2% (Table 154 of the SU lists the 14 patients who developed bradycardia (13 levetiracetam, placebo). Among the 4 patients with bradycardia from Study N051 all received levetiracetam 2000 mg/day, the highest dose in that study. Among the remaining 9 levetiracetam-treated patients all received the 3000 mg/day dose suggesting a possible dose effect.

With respect to the clincical significance of the bradycardia observed in the levetiracetam-treated patients 12 of the 13 patients had a baseline heart rate less than 60 bpm and the lowest end evaluation heart rate was 42 bpm.

I reviewed the vital signs measurements in healthy volunteers to see if there was any evidence of an effect of levetiracetam treatment on heart rate (SU pages 112 – 117).

In single dose studies 104 levetiracetam-treated patients and 35 placebo-treated patients had pre and post pulse measurements. When the post-dose value chosen was the "worst" value the mean pulse rates were 64.7 and 60.3 bpm when measured pre and post-levetiracetam, respectively. This represents a mean change of –4.4 bpm compared to –4.2 bpm for the placebo group.

In a double blind, placebo-controlled, ascending dose study 6 patients received levetiracetam (500 mg, 1000 mg, 2000 mg, 3500 mg, and 5000 mg) and 2 patients received placebo each day. Pulse was measured pre-dose and 0.5, 1, 1.5, 2.5, 3, 3.5, 4, 6, 8, 12, and 24 hours post dose. Using repeated measures analysis of covariance there was no statistically significant difference in pulse between the treatment groups.

In multiple dose studies 155 levetiracetam-treated patients and 76 placebo-treated patients had pre and post-dose pulse measurements. When the post-dose value chosen was the "worst" value the mean pulse

rates were 68.4 bpm and 65.0 bpm when measured pre and post levetiracetam, respectively. This represents a mean change of –3.4 bpm compared to 0.0 for the placebo group.

In a double blind placebo-controlled multiple dose study (N061) 12 patients received levetiracetam 1500 mg/day and 4 patients received placebo for 13 days. Heart rate was measured by ECG 1,2 and 8 hours after the morning dose and prior to retiring daily. Using repeated measures analysis of covariance there was no statistically significant differences in pulse between the treatment groups.

8.9.4 Controlled Trials of Other Indications: Baseline and end of Evaluation Analysis

For the ECG data from the three controlled studies in anxiety (473 levetiracetam, 242 placebo-treated) there did not appear to be any notable changes from baseline for QRS, PR, QTc or heart rate when comparing the levetiracetam and placebo groups.

With respect to heart rate there was a decrease from baseline in levetiracetam-treated patients of –0.3 bpm compared to a decrease from baseline in placebo-treated patients of –1.3 bpm. When examining heart rate by shift analyses 6.1% and 5.4% of patients went from normal heart rates to bradycardia for the levetiracetam and placebo groups, respectively. In the levetiracetam-treated patients 4.9% had a PCS decrease in heart rate compared to 8.3% in the placebo group.

8.10 Additional Analyses and Explorations: Neurotoxicity

The sponsor has undertaken a review of the adverse event profile to identify any safety concerns of clinical significance. When reporting on the results in controlled adult epilepsy studies I have chosen to include both periods of crossover Study N051. In no instance did results differ markedly when only the first period of Study N051 is considered.

8.10.1.1 Somnolence and Asthenia

The sponsor begins the discussion of adverse events associated with neurotoxicity on page 317 of the SU. In adult epilepsy patients participating in controlled trials (both crossover periods of Study N051), somnolence was reported in 114 (14.8%) of levetiracetam-treated patients and asthenia in 113 (14.7%) of levetiracetam-treated patients. In comparison, among placebo-treated patients 37 (8.4%) and 40 (9.1%) reported somnolence and asthenia, respectively. Somnolence and asthenia occurred early in treatment, and somnolence appeared to be dose related.

The sponsor has attempted to capture all somnolence-related events using the UCB grouping of COSTART terms "Sedation". This grouping includes hangover effect, somnolence, and stupor. The sponsor notes that on further review of patients with the reported term "stupor" none met the strict medical definition for this term (partial or nearly complete unconsciousness). Results for the UCB grouping of adverse events for sedation are presented below (sponsor's Table 158A, SU Vol. 2, p 318). The incidence of sedation and asthenia is greater in the levetiracetam treated-patients in all controlled studies (Table 74). In the controlled epilepsy studies 23 (3.0%) of levetiracetam-treated patients discontinued and 2 (0.3%) had a serious adverse event for sedation. In comparison 4 (0.9%) placebo-treated patients discontinued and none had a serious event. With respect to asthenia 6 (0.8%) of levetiracetam-treated patients discontinued and none had a serious event. In comparison 2 (0.5%) of placebo-treated patients discontinued and none had a serious adverse event for asthenia..

Table 74: Incidence of Somnolence and Asthenia in Controlled Studies of Levetiracetam

Placebo-controlled Studies in Epilepsy, Cognition, and Anxiety (Adult Patients)

UCB Adverse Event Grouping Term / Preferred Term	Epilepsy Studies (both periods of N051)		Cognition		Anxiety	
	Levetiracetam (N = 769)	Placebo (N = 439)	Levetiracetam (N = 394)	Placebo (N = 344)	Levetiracetam (N = 1084)	Placebo (N = 525)
Sedation	114 (14.8%)	38 (8.7%)	47 (11.9%)	23 (6.7%)	73 (6.7%)	9 (1.7%)
Hangover effect	0	0	0	0	1 (0.1%)	0
Somnolence	114 (14.8%)	37 (8.4%)	47 (11.9%)	22 (6.4%)	70 (6.5%)	9 (1.7%)
Stupor	1 (0.1%)	1 (0.2%)	2 (0.5%)	1 (0.3%)	2 (0.2%)	0
General Symptoms and Complaints[a]	165 (21.5%)	62 (14.1%)	68 (17.3%)	50 (14.5%)	86 (7.9%)	32 (6.1%)
Asthenia	113 (14.7%)	41 (9.3%)	61 (15.5%)	41 (11.9%)	53 (4.9%)	16 (3.0%)

[a] Other general symptoms and complaints are malaise, pain, chills, sweating, pallor, and thirst

8.10.1.2 Coordination Difficulties

The UCB grouping of adverse events for "coordination difficulties" includes the COSTART terms abnormal gait, ataxia, cerebellar syndrome, and incoordination. Coordination difficulties occurred in 26 (3.4%) of levetiracetam–treated patients compared to 7 (1.6%) of placebo-treated patients in controlled adult epilepsy studies (sponsors Table 159A, SU, Vol. 2, p 320). In the controlled epilepsy studies 3 (0.4%) of levetiracetam-treated patients discontinued for coordination difficulties and 1 (0.1%) had a serious adverse event for ataxia. In comparison none of the placebo-treated patients discontinued or had a serious adverse event for coordination difficulties.

Table 75: Incidence of Coordination Difficulties in Adult Epilepsy Studies

Incidence of Coordination Difficulties in Adult Epilepsy Studies

Part 1: Both Crossover Periods (ISS Presentation)

UCB adverse event Grouping Term / Preferred Term	Placebo-controlled Studies (both periods of N051)		
	Baseline (N = 1023)	Levetiracetam (N = 769)	Placebo (N = 439)
Coordination difficulties	11 (1.1%)	26 (3.4%)	7 (1.6%)
Abnormal gait	2 (0.2%)	5 (0.7%)	2 (0.5%)
Ataxia	8 (0.8%)	20 (2.6%)	5 (1.1%)
Cerebellar syndrome	0	0	0
Incoordination	2 (0.2%)	3 (0.4%)	2 (0.5%)

[a] 95% confidence interval about the difference in incidences between levetiracetam and placebo does not encompass zero

8.10.1.3 Cognitive Effects

The UCB grouping of adverse events for "cognitive symptoms" includes the COSTART terms amnesia, confusion and thinking abnormal. In the adult controlled epilepsy studies (3.6%) of levetiracetam-treated patients and (2.7%) of placebo-treated patients had a cognitive effects adverse event. (sponsor's Table 160A., SU, Vol. 2, p 321). Among all adult epilepsy patients approximately 10% had a "cognitive symptoms" adverse event. In the controlled epilepsy studies 4 (0.5%) of levetiracetam-treated patients discontinued for cognitive effects and none had a serious adverse reaction. In comparison 3 (0.7%) of placebo-treated patients discontinued for cognitive effects and 2 had a serious adverse reaction.

8.10.1.4 Movement Disorders

The UCB grouping of adverse events for "movement disorders" includes the COSTART terms dyskinesia, hyperkinesia, movement disorder, myoclonus, torticolis, tremor, and twitching. In the adult controlled epilepsy studies the incidence of movement disorders was 2.0% and 2.5% among levetiracetam and

placebo-treated patients, respectively. The majority of events in the "movement disorders" grouping were due to tremor. In all adult epilepsy patients 8% had a "movement disorders" adverse event. In the controlled epilepsy studies no patients discontinued due to a movement disorder.

8.10.1.5 Paralysis

The UCB grouping of adverse events for "paralyses" includes the COSTART terms Babinski sign positive, facial paralysis, hemiplegia, hypertonia, paralysis, and reflexes decreased. In the adult controlled epilepsy studies the incidence of movement disorders was 0.7% and 0.5% among levetiracetam and placebo-treated patients, respectively. In all adult epilepsy patients 2.9% had a "paralyses" adverse event. Drug was discontinued in patient **174** (participating in an open-label Study N035) as a result of hemiplegia related to glioblastoma multiforme.

8.10.1.6 Peripheral Nerve Symptoms

The UCB grouping of adverse events for "peripheral nerve symptoms" includes the COSTART terms circumoral parasthesia, hyperesthesia, hypotonia, neuralgia, neuritis, neuropathy, parasthesia, peripheral neuritis, reflexes decreased. In the adult controlled epilepsy studies the incidence of peripheral nerve symptoms was 2.9% and 2.8% among levetiracetam and placebo-treated patients, respectively. In all adult epilepsy patients 8.5% had "peripheral nerve symptoms" adverse event. Drug was discontinued in 7 patients, 4 as a result of paresthesia, and 1 each due to hypesthesia, hypotonia, neuralgia, and neuropathy. Three of these events were considered serious, patients **4926**, **3040**, and **3121**.

8.10.1.7 Speech Disorders

The UCB grouping of adverse events for "speech disorders" includes the COSTART terms aphasia, dysarthria, speech disorder, and voice alteration. In the adult controlled epilepsy studies the incidence of speech disorders was 0.8% and 1.8% among levetiracetam and placebo-treated patients, respectively. In all adult epilepsy patients 3.9% had a "speech disorders" adverse event. Drug was discontinued/dose reduced in 7 patients, 4 as a result of dysarthria and 3 as a result of speech disorder. Patient 2144 had a serious adverse event of dysphasia attributed to progression of her brain tumor.

8.10.1.8 Vertigo/Dizziness

The UCB grouping of adverse events for "vertigo/dizziness" includes the COSTART terms dizziness and vertigo. In the adult controlled epilepsy studies the incidence of vertigo/dizziness was 11.6% and 5.2% among levetiracetam and placebo-treated patients, respectively (sponsor's Table 169A, SU, Vol. 2, p 328). In the sponsor's opinion, based upon observations from the clinical pharmacology studies and Studies N051, N052, N0132, this adverse event is possibly dose-related. In the controlled epilepsy studies 4 (0.5%) of patients discontinued levetiracetam for vertigo/dizziness and 2 (0.3%) had a serious adverse event. In comparison none of the placebo-treated patients discontinued or had an adverse event for vertigo/dizziness.

8.10.1.9 Vision Abnormalities

The UCB grouping of adverse events for "vision abnormalities " includes the COSTART terms abnormal vision, abnormality of accommodation, amblyopia, blindness, diplopia, refraction disorder, and visual field defect. In the adult controlled epilepsy studies the incidence of vertigo/dizziness was 4.2% and 3.7% among levetiracetam and placebo-treated patients, respectively. In the controlled epilepsy studies 1 (0.1%) of levetiracetam-treated patients discontinued for vision abnormalities and none had a serious adverse event. In comparison none of placebo-treated patients discontinued or had a serious adverse event fo a vision abnormality. In all adult epilepsy patients 9.6% had a "vision abnormalities" adverse event. The sponsor reviewed the individual cases and states that there was no evidence of any patients with progressive visual field defects. Drug was discontinued/dose reduced in 5 patients, 4 as a result of amblyopia and 1 as a result of abnormal vision. Patients **1756** and **2263** had a serious adverse event attributed to diplopia.

8.10.2 Additional Analyses and Explorations: Psychiatric Adverse Events

The sponsor has undertaken a review of psychiatric adverse events in an effort to distinguish whether these events are related to treatment or to the underlying disease being treated. Once again the sponsor has created UCB groupings of COSTART terms to capture psychopathological entities. The UCB groupings are:

- **Psychotic symptoms**: delusions, hallucinations, manic reaction, paranoid reaction, psychosis, and psychic depression;
- **Nonpsychotic/behavioral**: agitation, anti-social reaction, anxiety, apathy, depersonalization. depression, emotional lability, euphoria, hostility, nervousness, neurosis, and personality disorder;
- **Auto-aggressive behavior**: intentional overdose and suicide attempt;
- **Sleep disorders**: abnormal dreams, insomnia, and sleep disorder.

Among 3347 patients in all clinical trials 23 (0.7%) reported psychotic symptoms, 504 (15%) reported nonpsychotic behavioral symptoms, 14 (0.4%) reported auto-aggressive behavior, and 185 (5.5%) reported sleep disorder.

The incidence of psychiatric adverse events in controlled trials of epilepsy and other indications is presented in Table 76 (sponsors Table 173A, SU, Vol. 2, p 332). The most commonly reported symptoms were those grouped into the nonpsychotic behavioral category. Epilepsy studies had a higher overall incidence and a greater difference between the levetiracetam and placebo-treated patients (13.5% vs. 6.0%). Psychotic symptoms were reported much less frequently. In epilepsy studies 5 (0.7%) of levetiracetam-treated patients and 1 (0.3%) placebo patients had a "psychotic symptoms" adverse event. Seven auto-aggressive events were reported all in levetiracetam-treated patients (3 in epilepsy studies and 2 in anxiety studies). In the controlled epilepsy studies 13 (1.7%) of levetiracetam-treated patients discontinued for nonpsychotic/behavioral events and 6 (0.8%) had a serious adverse event. In comparison 1 (0.2%) of placebo-treated patients discontinued for nonpsychotic/behavioral events and one had a serious adverse event.

Table 76: Incidence of Psychiatric Events in Controlled Levetiracetam Studies

Incidence of UCB Adverse Event Grouping Terms for Psychiatric Events – Placebo-Controlled Studies in Epilepsy*, Cognition, and Anxiety (Adults)

UCB Adverse Event Grouping Term Preferred Term	Epilepsy Studies		Cognition		Anxiety	
	Levetiracetam (N = 672)	Placebo (N = 351)	Levetiracetam (N = 394)	Placebo (N = 344)	Levetiracetam (N = 1084)	Placebo (N = 525)
Psychotic Symptoms	5 (0.7%)	1 (0.3%)	0	0	2 (0.2%)	1 (0.2%)
Nonpsychotic Behavioral Symptoms	91 (13.5%)	21 (6.0%)	25 (6.3%)	14 (4.1%)	56 (5.2%)	29 (5.5%)
Auto-Aggressive Behavior	3 (0.4%)	0	1 (0.3%)	0	2 (0.2%)	0
Sleep Disorders	24 (3.6%)	10 (2.8%)	18 (4.6%)	17 (4.9%)	55 (5.2%)	11 (2.1%)

* Only first period of Study N051 included.

The sponsor undertook further analysis of psychiatric adverse events in controlled trials of epilepsy patients to examine the relationship of these symptoms with gender, age, concomitant use of phenytoin, concomitant use of phenobarbital, concomitant use of vigabatrin, pre-study history of psychiatric problems, and report of depression during baseline. The analysis was done using a logistic regression model.

A pre-study history of psychiatric disorder and use of phenytoin had a statistically significant association with the occurrence of a nonpsychotic behavioral symptom.

Additionally, for the levetiracetam group the relationship between dose and incidence of a nonpsychotic behavioral symptom was examined (Table 77). There is no linear trend with dose of levetiracetam. An increase from 6 to 19% is noted for the last two dose groups, however there were only 36 patients exposed to the highest levetiracetam dose.

Table 77: Incidence of Nonpsychotic/behavioral Adverse Event by Dose: Adequate and Well-controlled Epilepsy Studies

Dose (mg/day)	Number of Patients	Number (%) of Patients with Nonpsychotic/Behavioral Symptoms during Treatment
0 < dose ≤ 1000	216	30 (13.9%)
1000 < dose ≤ 2000	170	38 (22.4%)
2000 < dose ≤ 3000	250	16 (6.4%)
3000 < dose ≤ 4000	36	7 (19.4%)
Total	672	91 (13.5%)

based on sponsor's Table 174, SU, Vol. 2, p 334

8.11 Additional Analyses and Explorations: Allergic Reactions

The sponsor begins discussion of allergic reactions on page 368 of the SU. In order to capture all adverse events indicative of an allergic reaction several COSTART preferred terms were examined (Table 78).

Table 78: Number of Patients Receiving Levetiracetam and Experiencing Adverse Events Potentially Indicative of Allergic Reaction in Adult and Pediatric Epilepsy Studies

Event	Number of Subjects			
	Total	DC or Dose ↓	Serious	Severe
ADULT EPILEPSY PATIENTS				
Allergic reaction	26	0	0	0
Photosensity reaction	16	1	0	0
Tongue edema	1	0	0	0
Asthma	21	1	1	1
Larynx edema	1	0	0	0
Erythema multiforme	1	0	0	0
Exfoliative dermatitis	3	0	0	0
Maculopapular rash	4	1	1	0
Petechial rash	1	0	0	0
Pruritis	28	1	0	3
Rash	107	3	2	0
Urticaria	7	1	0	0
Vesiculobullous rash	8	0	0	0
PEDIATRIC EPILEPSY PATIENTS				
Maculopapular rash	1	0	0	0
Pruritis	1	0	0	0
Pustular rash	1	0	0	0
Rash	3	1	1	0
Vesiculobullous rash	1	0	0	0

based on sponsor's Table 19, SU, Vol. 2, p. 372

During the controlled epilepsy studies the sponsor identified 3 patients (**3016**, **2734**, and **2783**) with allergic reactions leading to discontinuation. Patient **3016** has already been discussed in the discontinuation section. Patient **2734**, a 40 y/o female received levetiracetam 500 mg/d for 181 days when she developed a rash. From the brief narrative summary it appears that the rash actually developed while she was participating in extension study N129. Patient **2783** a 28 y/o male was receiving levetiracetam 4000 mg/day for 160 days when he discontinued in the open-label portion of Study N052 because of a very itchy rash on the arms chest and back. He had 2 occurrences of rash during the double blind portion of the study from which he apparently recovered while continuing levetiracetam treatment.

One pediatric patient discontinued because of a rash. Patient 4876, a 11 y/o female was receiving levetiracetam 2250 mg/day for 323 days when she developed a maculopapular rash on both upper arms the left shin and the left upper chest. Study medication was withdrawn and the rash resolved after 22 days.

One adult patient is reported with an adverse event of erythema multiforme. I requested the CRF Adverse Event Report form for this patient. The patient is described as having welts on the arms and legs, swelling of the hands and feet, and itching. The report specifically mentioned that no rash or mucosal lesions were noted. The reaction is reported to have resolved with benadryl. From the adverse event report it appears that this patient most likely had urticaria rather than erythema multiforme.

8.12 Withdrawal Phenomenon and Abuse Potential

The sponsor states that there have been no reports of drug abuse or any patterns of drug use to suggest abuse liability (SU, Vol. 2, p. 446). The sponsor summarizes a rat study suggesting that levetiracetam administered in doses up to 1800 mg/kg/day demonstrated no physical dependence.

8.13 Human Reproduction Data

The sponsor knows of 18 pregnancies in the levetiracetam development program of which 15 were exposed to levetiracetam (SU, Vol. 2, p 383). Among the pregnancies, 6 resulted in full term deliveries (1 set of twins) with all infants characterized as normal. One patient participating in Study N138 was diagnosed as being pregnant, withdrew from the study and was lost to follow-up.

Three pregnancies were terminated by spontaneous abortions, three pregnancies were terminated by elective abortions, 1 pregnancy was an ectopic, and in 4 pregnancies the outcome is unknown. Two of the three patients with spontaneous abortions are reported to have a previous history of spontaneous abortions. One of these fetuses had possible trisomy.

8.14 Overdose

The sponsor begins discussion of overdose on page 446 of the SU. The sponsor defined overdose as any dose exceeding 60 mg/kg/day. Such a dose is equivalent to 4200 mg/kg in a 70-kg person. The sponsor states that there have been no true toxic overdoses with levetiracetam based on the fact that the highest known dose of levetiracetam was 6000 mg/day. Other than drowsiness than was no other adverse sequelae in this patient.

A total of 34 patients in the levetiracetam development program were reported with a treatment-emergent adverse event of overdose (30 levetiracetam-treated, 4 placebo-treated). Eight levetiracetam-treated patients had an "accidental overdose". None led to serious sequelae. Six levetiracetam-treated patients had an intentional overdose/suicide event. Five of the six intentional overdose events were for concomitant medications. Seventeen levetiracetam-treated patients were reported with the adverse event "overdose". Fourteen of the 17 events were attributed to another antiepileptic drug or concomitant drug toxicity.

8.15 Drug-Drug Interactions

The sponsor begins discussion of drug interactions on page 411 of the SU. The sponsor reports that no drug interactions were identified for phenytoin, digoxin, oral contraceptives, warfarin and probenicid. For a complete review of the sponsor's pharmacokinetic studies examining drug interactions please see the attached review of Hong Zhao, Ph.D, Office of Clinical Pharmacology and Biopharmaceutics. Dr. Zhao,s conclusions concur with those of the sponsor.

The sponsor explored adverse event risk by concomitant antiepileptic drug use. The number of patients receiving a single antiepiletic drug in addition to levetiracetam was 46 for valproate, 190 for carbamazipine and 23 for phenytoin.

The sponsor reports that a qualitative review of the adverse events showed the incidence of adverse events was similar in patients who received either valproic acid, carbamazipine, or phenytoin as a single agent in combination with levetiracetam when compared with the overall population for each other. Exceptions

were a higher incidence of ecchymosis, convulsions, coordination difficulties, vertigo dizziness, and accidental injury in the phenytoin alone group compared to the carbamazipine alone and valproate alone groups. In contrast, GI symptoms and infections were slightly more frequent in valproate-treated patients compared to the phenytoin and carbamazipine-treated patients. The sponsor concludes that there is no evidence to suggest that combination of levetiracetam with either valproate, carbamazipine, or phenytoin results in a higher incidence of any specific adverse event.

8.16 Drug-Disease and Drug-Demographic Interactions

The sponsor begins discussion of drug-disease and drug-demographic interactions on page 422 of the SU. The half-life of levetiracetam is increased in subjects with renal impairment. The half-life is shorter and the clearance higher in children. For a complete review of the sponsor's pharmacokinetic studies examining drug-disease and drug-demographic interactions please see the attached review of Hong Zhao, Ph.D, Office of Clinical Pharmacology and Biopharmaceutics. Dr. Zhao concludes that except for renally impaired patients and patients undergoing hemodialysis, there is no dosage adjustment necessary for hepatic impairment, gender of race.

9 Safety Conclusions

9.1 Animal Pharmacology and Toxicology

Levetiracetam has a favorable toxicologic profile. Single dose studies indicate low acute toxicity. Repeat dose studies of levetiracetam were well tolerated. In general clinical signs were minimal across studies and species.

9.2 Human Pharmokinetic Considerations

Levetiracetam has a favorable pharmacokinetic profile. Levetiracetam is rapidly and almost completely absorbed after oral administration and bioavalilability is not affected by food.. The pharmacokinetics are linear. Levetiracetam is not protein bound ($\leq$ 10% bound). In humans 66% of the dose is excreted unchanged in the urine and dosing adjustments only have to be made for patients with impaired renal function. The major metabolite (ucb L057), accounting for 24% of the dose has no pharmacologic activity. Levetiracetam is not liver cytochrome P450 dependent and there is minimal potential for pharmacokinetic drug interactions

9.3 Human Exposure

The number of subjects exposed to levetiracetam in the N999 database is adequate. All long-term adult exposure derives from the adult epilepsy studies (1008 patients for greater than six months and 642 patients for greater than 1 year). Exposure to levetiracetam at doses greater than 2500 mg/day is more limited (783 patients greater than 6 months and 518 greater than 1 year). However, this level of exposure exceeds ICH Guidelines even at doses $\geq$ 2500 mg/day (300 to 600 patients treated for 6 months, 100 patients exposed for a minimum of 1 year). Overall, there are 2449 person-years of exposure to levetiracetam in the entire development program and 2257 person-years of exposure when only considering epilepsy patients. While this level of exposure represents a significant experience with levetiracetam it is still insufficient to assess the occurrence of rare adverse events.

The sponsor's Safety Update volumes 463 - 584 includes all safety data in the N999 clinical database up to November 30, 1998 and serious adverse event data up to February 28, 1999. As of November 30, 1998, treatment was ongoing for 617 patients. For serious adverse events approximately 400 patient-years of exposure would accrue through October of 1999 assuming all 617 patients continue treatment up until that date.

9.4 Deaths

Exposure to levetiracetam did not appear to be associated with an increased mortality risk. The mortality for all levetiracetam-treated epilepsy patients was 9.3 per 1000 person years. In controlled studies in epilepsy the mortality for levetiracetam-treated patients was 10.7 per 1000 person-years compared to 13.9 per 1000 person-years for placebo-treated patients. The cause specific mortality due to SUDEP was 3.7 per 1000 person-years which is similar to rate observed for other antiepileptic drugs (lamotrigine 3.5, gabapentin 3.8, and tiagabine 3.9 per 1000 person-years).

A potential mortality signal in controlled non-epilepsy studies was seen that was not less significant after removal of 3 cancer deaths who died more than 30 days after discontinuation of levetiracetam and whose precipitating event appeared unrelated to study treatment.

Two patients had suicide deaths and are summarized below. Patient 728, a 45 y/o female had a personal history of depression and strong family history of suicide (mother and brother both committed suicide). In addition she was on levetiracetam for only 4 days. The circumstances surrounding the suicide of patient 2940 are less clear.

728 This 45 y/o female with a history of depression and family history of suicide was receiving levetiracetam 1000 mg/day for 4 days when she discontinued levetiracetam because of nausea and vomiting. On review of her medications she had taken 28 250mg capsules rather than 16 capsules over the 4 day period that should have been taken if she had taken study medication as directed. The patient began complaining of suicidal thoughts the day after discontinuing levetiracetam. The patient was scheduled for psychiatric hospitalization 10 days after discontinuing levetiracetam. She committed suicide the evening prior to her scheduled hospitalization.

2940 This 43 y/o male was receiving levetiracetam 3000 mg/day for 128 days when he successfully committed suicide. Additional details are not provided in the narrative. Review of the CRF notes the patient cut his forearm veins and that symptoms of depression were not observed during administration of study medication. However, mention is made that the patient was having marital and financial problems.

9.5 Adverse Event Coding

The coding of adverse events, with noted exceptions, appeared appropriate. The sponsor's grouping of COSTART terms into clinically meaningful categories was helpful in describing the safety profile of levetiracetam. The descriptions of deaths, discontinuations, and serious adverse events in the narrative summaries were generally adequate

9.6 Adverse Events

Levetiracetam was associated with several commonly occurring adverse events (observed in at least 5% of exposed patients). These events included somnolence (22.1%), asthenia (22.2%), dizziness (17.9%), depression (9.8%), and ataxia (5.7%). Levetiracetam-treated subjects experienced an increased incidence of these events compared to placebo in controlled epilepsy trials (somnolence (14.9% vs. 9.7%), asthenia (14.1% vs. 9.7%), dizziness (9.2% vs. 4.3%), depression (4.0% vs. 2.3%) and ataxia (2.6% vs. 1.1%). Somnolence, asthenia and dizziness appear to occur earlier in treatment. Only somnolence appeared to be related to dose. These adverse events did not appear to be associated with substantial risk to patients as the symptoms generally improved with continued treatment, dose reduction or discontinuation.

A disproportionate number of discontinuations due to behavioral related events in the controlled and uncontrolled epilepsy studies were noted by the sponsor and me. The sponsor created a grouping of COSTART terms to capture these related events under the rubric nonpsychotic/behavioral events. In the controlled epilepsy trials 13.5% of levetiracetam-treated patients had such and event compared to 6.0% of placebo patients. In the controlled epilepsy studies 13 (1.7%) of levetiracetam-treated patients discontinued for nonpsychotic/behavioral events and 6 (0.8%) had a serious adverse event. In comparison 1 (0.2%) of placebo-treated patients discontinued for nonpsychotic/behavioral events and 1 (0.2%) patient had a serious adverse event.

It must be kept in mind that a post hoc grouping of adverse events could lead to an artifactual difference between levetiracetam-treated and placebo-treated patients. However, in reviewing these discontinuations there appears to be a related behavioral disturbance among these patients that in many instances resolves in 1 to 2 weeks following discontinuation of levetiracetam.

The sponsor conducted additional analyses of psychiatric adverse events in order to identify risk factors for the occurrence of these events. A pre-study history of psychiatric disorder and concomitant use of phenytoin had a statistically significant association with these events. The finding of a relationship with phenytoin is of uncertain significance. In addition the sponsor examined the relationship of levetiracetam dose to nonpsychotic/behavioral events and did not find a clear dose response relationship.

In the controlled epilepsy trials more rashes were reported on placebo than levetiracetam. Only one patient had a rash on levetiracetam treatment. Based on the dermatological consultation this rash did not appear to be severe and while the relationship to study drug was considered possible is not definitive given the patient's exposure to other drugs including lamotrigine. In the adult epilepsy studies (excluding the controlled studies) one levetiracetam-treated patient was reported to have erythema multiforme, however after review of the CRF it appeared the patient had urticaria. There were no discontinuations or serious

adverse events in adult epilepsy studies that appeared to represent events of particular concern (e.g., toxic epidermal necrolysis, Steven's Johnson Syndrome or, exfoliative dermatitis).

9.7 Laboratory

In controlled trials of epilepsy 11 (1.4%) of levetiracetam-treated and 6 (1.4%) of placebo-treated patients had a possibly clinically significant liver enzyme test. None of the levetiracetam-treated patients had an elevated AST value and only one patient had a mildly elevated bilirubin (2.2 mg/dl) which decreased with continued treatment (1.8 mg/dl).

In all adult epilepsy patients (excluding patients already identified in controlled epilepsy studies) none of the patients with a PCS ALT, AST, GGT, or alkaline phosphatase had a concomitant elevation of total bilirubin. Among the 3 patients with a PCS elevated total bilirubin patients **2138** and **2600** had isolated elevations of 2.6 mg/dl and 2.3 mg/dl, respectively. Patient **3112** had persistent though mild elevations of total bilirubin while receiving levetiracetam 3000 mg/day from 12/11/97 (2.3 mg/dl) through the last reported value on 7/30/98 (2.3 mg/dl). None of the patients with elevated total bilirubin had concomitant elevations of other liver enzymes.

Four patients in adult epilepsy studies (excluding controlled studies) discontinued because of elevated liver enzymes. Patient **2321** had an elevation of liver enzymes that normalized after the discontinuation of both valproate and levetiracetam therefore confounding any causality assessment. Patient **2617** had an elevated GGT and was subsequently discontinued because of excessive alcohol intake. In two patients (**1582** and **2791**) there was a suggestion of a temporal relation between levetiracetam and elevated liver enzymes. Patient **1582** had a significantly elevated GGT at baseline (731 IU/L) that peaked at 1827 IU/L after 577 days of treatment then returned towards the baseline value on discontinuation. Patient **2791** had elevated alkaline phosphatase, GGT, AST and ALT that returned towards normal with discontinuation of levetiracetam. However, the patient had a mild elevation of ALT and GGT at baseline. Patient 2791 is summarized below. Neither patient had a possibly clinically significant elevation of total bilirubin.

2791 This 37 y/o female was receiving levetiracetam for 182 days when she was noted to have a significant rise in liver enzymes (ALT256 U/L, AST 116 U/L, GGT 126 U/L, and alkaline phosphatase 259 U/L). The patient was hospitalized on 06/19/96 for further investigation of elevated liver enzymes. Levetiracetam dosage was decreased to 1000 mg/day and an ultrasound of the abdomen was reported as normal. Levetiracetam was discontinued and enzymes returned towards baseline. Concomitant antiepileptic medication at the time of the event was carbamazipine 600 mg/day, which the patient had taken since 1993.

Date	Levetiracetam mg/day	Total Bilirubin mg/dl (normal 0.2-2.0)	Alkaline Phos. U/L (normal 73-207)	GGT U/L (normal 5-25)	AST U/L (normal 0-21)	ALT U/L (normal 0-21)
09 06 95	baseline	0.8	188	40	20	32
04 10 96	3000	0.3	222	51	46	95
05 17 96	3000	0.6	259	126	116	256
07 01 96	levetiracetam discontinued					
07 15 96		0.8	190	47	26	48

In controlled trials of epilepsy 37 (4.8%) of levetiracetam-treated and 15 (3.4%) of placebo-treated patients had a possibly clinically significant low hematocrit. The lowest hematocrit during the controlled trials was 29% in patient **1974**, a 21 y/o female who also had an adverse event reported for menorrhagia. She continued in an extension study for 419 days with a final hematocrit of 26%.

In controlled trials of epilepsy 16 (2.1%) of levetiracetam-treated and 6 (1.4%) of placebo-treated patients had a possibly clinically significant low neutrophil count. Four patients still had a low neutrophil count at completion of the controlled trial but continued treatment in extension studies. All four patients had final values in the extension studies that were no longer PCS low.

In all adult epilepsy studies (excluding controlled studies) 2 patients (**2426** and **2551**) discontinued for decreasing neutophil counts that were not less than 1.0 x 10^9/L. Two patients had serious adverse events reported for leukopenia. Patient **176** had a decrease in leukocytes to 3.4 x 10^9/L which increased to 4.0 x 10^9/L with continued therapy. Patient **2135** had a PCS low neutrophil count of 0.6 x 10^9/L which increased with a dose reduction. The patient was discontinued from levetiracetam shortly thereafter because it was not felt to be helping her seizure disorder.

In the Named Patient Use program patient **001/009** had a decrease in neutrophils to 0.82 x 10^9/L that was still low 5 days after discontinuation of levetiracetam. The patient was seen by a hematologist and underwent bone marrow examination. She reportedly has a history of cyclical low neutrophil counts.

In trials for other indications two patients (**4114** and **4192**) had a decline in neutrophils to 0.6 x 10^9/L after 28 days of levetiracetam treatment. Patient **1613** had a 15 day post-treatment neutrophil count of 0.17 x 10^9/L . The sponsor is attempting to obtain additional follow-up on these patients as well as patient 001/009.

Interpretation of neutropenia in levetiracetam-treated patients participating in the he adult epilepsy studies is clouded by the use of concomitant antiepileptic medications which may cause neutropenia. While several patients in adult epilepsy studies developed clinically significant neutropenia (less than 1.0 6 x 10^9/L) all resolved with dose reduction or continued treatment. In addition in the controlled epilepsy studies 1.4% of placebo-treated patients developed neutropenia compared to 2.1% of levetiracetam treated patients. None of the hematologic adverse events in the adult epilepsy patients appeared to represent events of pancytopenia, or aplastic anemia however, the above cases with unresolved neutopenia from the trials of other indications and Named Patient Use Program raises some level of concern.

9.8 Electrocardiogram Data

ECG data from the 3 of the controlled epilepsy studies (Studies N051, N132, and N138) were carefully re-analyzed for any changes from baseline to end evaluation. More levetiracetam-treated patients had normal heart rate at baseline and bradycardia ($\leq$ 60 bpm) at end evaluation than placebo-treated patients (levetiracetam – placebo = 5.8%). When the sponsor examined bradycardia of $\leq$ 50 bpm 13 (2.2%) of levetiracetam and 1(0.3%) of placebo-treated patients were normal at baseline and had bradycardia at the end of baseline.

A cardiologist reviewed and identified all treatment-emergent abnormal ECGs. Bradycardia developed in 13(2.2%) of levetiracetam-treated patients. Among the 4 patients with bradycardia from Study N051 all received levetiracetam 2000 mg/day, the highest dose in that study. Among the remaining 9 levetiracetam-treated patients all received levetiracetam 3000 mg/day, also the highest treatment dose, suggesting a possible dose effect.

ECG data from 3 controlled studies in other indications (Studies N043, N044, N045) was also analyzed, however intervals were not re-measured for this analysis. When examining heart rate 6.1% and 5.4% of patients went from normal heart rates to bradycardia ($\leq$ 60 bpm) for the levetiracetam and placebo-treated patients, respectively.

Heart rate measurements from clinical pharmacology studies in healthy volunteers were reviewed and did not indicate a consistent effect of levetiracetam on heart rate. In the controlled epilepsy studies levetiracetam appears to cause mild bradycardia of uncertain clinical significance.

9.9 Other Issues

Levetiracetam was investigated as preventative therapy for deep venous thromboembolism in patients undergoing major elective surgery in Study N099. The rational for proceeding with Study N099 relates to 3 open-label studies (N093, N079, and N082) in healthy volunteers. Levetiracetam (250 mg, 500 mg, or 1000 mg) was given 12 hours after aspirin 20 mg. Bleeding time was measured at baseline, prior to administration of levetiracetam, and 2 and 12 hours post-levetiracetam dose. There were 3.5% to 17%

increases and 12.5% to 30% increases in bleeding time 2 and 12 hours post-levetiracetam, respectively. However no dose response relationship was observed and no bleeding times exceeded the normal range. In Studies N102 and N108, double-blind, placebo-controlled multiple dose crossover studies no change in bleeding time was observed 24 hours after the final dose. Based on the results of these studies the sponsor terminated Study N099 after enrollment of 6 patients.

Based on the review of the data submitted, levetiracetam appears to be reasonably safe when used as recommended.

10 Recommendations

In the opinion of this reviewer, NDA 21-035 is approvable from a clinical standpoint.

/S/

Joel Freiman, MD, MPH
Division of Neuropharmacological Drug Products

cc: NDA 21-035/Freiman/Katz/Malandrucco

11 Appendix 1

Table 1
Overview of Data Sources for the Integrated Summary of Safety
(Data Cut-off 30 June 1998)

A: Clinical Pharmacology Studies in Healthy Volunteers

Study No.	Principal Investigator	Country	Dates of Conduct	Status	Report Location in NDA (Vol. / Page No.) †
Single Dose Studies in Healthy Volunteers					
D002	Darragh	Ireland	11/86-2/87	Complete	76 / 661
N046	Fisher	United Kingdom	2-3/93	Complete	77 / 1054
N057	Peuvot	Belgium	6/85	Complete	140 / 432
N058	Peuvot	Belgium	1985	Complete	141 / 787
N069	Scheen	Belgium	5/87-4/88	Complete	75 / 346
N076	Melon	Belgium	4/87-5/88	Complete	141 / 923
N124	Nutt	United Kingdom	11/93-2/94	Complete	152 / 4476
N201	Murasaki	Japan	12/95-4/96	Complete	78 / 1357
N203	Murasaki	Japan	9/96-5/97	Complete	109 / 11609
N206††	Keesal	United States	11/93	Complete	107 / 11153
Multiple Dose Studies in Healthy Volunteers					
N061	Herschuelz	Belgium	2-5/86	Complete	130 / 18914
N079††† N082††† N093††† N096††† N102††† N108†††	Schoonbrood	Belgium	10/87–2/90	Complete	149 / 3608
N128	Strobel	Germany	11-12/93	Complete	79 / 1814
N135	Weber	Germany	11/94-5/95	Complete	109 / 11892
N144	Meyerhoff	Germany	7-9/96	Complete	113 / 13037
N146	Weber	Germany	11/96-5/97	Complete	115 / 13829
N150	Mant	United Kingdom	1/97-3/97	Complete	123 / 16483
N202	Murasaki	Japan	9/96-3/97	Complete	81 / 2260
Single Dose Studies in Healthy Volunteers – Not Included in N999 Database					
N205	Peuvot	Belgium	7/85	Complete	75 / 207
N001	Rosadini/Sannita	Italy	10/80	Complete	129 / 18475
N002	Rosadini/Sannita	Italy	11/81	Complete	129 / 18712
N204	Rosadini	Italy	11/85-4/86	Complete	143 / 1532

† CRF tabulations and selected CRFs are provided electronically in NDA Sections 11 and 12, respectively.
†† Non-UCB-sponsored study
††† These six studies are reported in one abbreviated report. However, Study N079, N082, and N093 were designed as single dose studies and therefore exposure on these studies is counted in the single dose studies group.

Table 1 – continued

Overview of Data Sources for the Integrated Summary of Safety (Data Cut-off 30 June 1998)

B: Clinical Pharmacology Studies in Special Populations

Study No.	Principal Investigator (Number if multiple)	Country	Dates of Conduct	Status	Report Location in NDA (Vol. / Page No.)[†]
Studies in Elderly Subjects					
N080	Hermann	Germany	11-12/87	Complete	132 / 19447
N083	Coupez	Belgium	4-9/88	Complete	94 / 6653
N097	Herrmann	Germany	8-10/88	Complete	142 / 1156
Studies in Subjects with Renal Impairment					
N137	Multiple (3)	Belgium	10/94-6/95	Complete	96 / 7203
N145	Nilsson	Sweden	1/96-2/97	Complete	97 / 7768
N152	Bagon	Belgium	5-6/98	Complete	100 / 8735
Study in Subjects with Hepatic Impairment					
N139	Thomsen	Germany	9/95-12/96	Complete	102 / 9200
Sleep Study in Patients with Epilepsy					
N142	Nutt	United Kingdom	9/95-2/96	Complete	152 / 4476
Single Dose Cerebral Blood Flow Study in Elderly Subjects – Not Included in N999 Database					
N060	Rosadini	Italy	8/85-9/85	Complete	141 909

[†] CRF tabulations and selected CRFs are provided electronically in NDA Sections 11 and 12, respectively.

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Table 1 – continued

Overview of Data Sources for the Integrated Summary of Safety (Data Cut-off 30 June 1998)

C: Epilepsy Studies

Study No.	Principal Investigator (Number if multiple sites)	Country (Number if multiple)	Dates of Conduct	Status	Report Location in NDA (Vol. / Page No.)[†]
Adequate and Well-controlled Studies – Included in N999 Database					
N051	Multiple (62)	Multiple/Eur. (6)	10/93-10/95	Complete	190 / 17602
N052	Multiple (37)	U.K., Belgium	9/93-3/97	Complete	269 / 43846
N132	Multiple (41)	United States	9/94-3/96	Complete	155 / 5640
N138	Multiple (51)	Multiple/Eur. (11)	6/95-5/98	Complete	234 / 32572
Open Label Studies – Included in N999 Database					
N015	Kasteleyn	Netherlands	2/92-6/93	Complete	83 / 2756
N016	De Deyn	Belgium	3/91-7/92	Complete	287 / 50302
N017	Shorvon	United Kingdom	2/91-5/91	Complete	289 / 51144
N018	Marescaux	France	1/91-8/93	Complete	291 / 51802
N028 N029 N034	Paulus Kasteleyn Marescaux	Germany Netherlands France	10/91-3/93	Complete	143 / 1550
N030	Stodieck	Germany	2/92-12/92	Complete	145 / 2355
N031	Stodieck	Germany	7/91-6/92	Complete	147 / 2790
N047	Shorvon	United Kingdom	5-10/93	Complete	85 / 3509
N049	Rosadini	Italy	4/93-3/94	Complete	296 / 53566
N053 N123	Marescaux Shorvon	France United Kingdom	8/93-6/94	Complete	88 / 4510
N127	De Barsy	Belgium	2/94-5/95	Complete	297 / 54025
N143	Browne/Leppik	United States	12/95-8/97	Complete	90 / 5468
N153	Multiple (13)	Multiple / Eur. (2)/U.S.	1998	Complete	405 / 92861
Long-Term Extension Studies – Included in N999 Database					
N032	Shorvon	United Kingdom	7/91-10/92	Complete	304 / 56342
N035	De Deyn	Belgium	7/91-10/93	Complete	305 / 56761
N038	Stodieck	Germany	1/92-7/93	Complete	307 / 57613
N039	Multiple (5)	Multiple/Eur. (5)	10/92-9/94	Complete	309 / 58233
N126	Shorvon, De Deyn	U.K., Belgium	1/94-11/95	Complete	311 / 59116
N129	Multiple (93)	Multiple/Eur. (11)	12/93-6/98	Ongoing	359 / 76724
N133	Multiple (65)	Multiple/Eur. (5)	10/94-5/97	Complete	314 / 60211
N140	Multiple (35)	United States	4/95-4/97	Complete	329 / 65654
N141	Laskar	Belgium	11/94-3/98	Complete	356 / 75535
N147	Multiple (33)	United States	5/96-6/98	Ongoing	390 / 87378
N157	Pellock	United States	1-9/98	Ongoing	405 / 92996
Pediatric Epilepsy Study					
N151	Pellock	United States	9/97-9/98	Ongoing	107 / 10952
N130	Van Rijckevorsel-Harmant	Belgium	10/94-7/95	Complete	301 / 55317
Other – Not Included in N999 Database					
Named Patient Use (Belgium, Denmark, France, United Kingdom)				Ongoing[††]	451 / 110339

[†] CRF tabulations and selected CRFs are provided electronically in NDA Sections 11 and 12, respectively.
[††] All patients, except 4 in Denmark, have been transferred into Study N129 or discontinued treatment.

Table 1 – continued

Overview of Data Sources for the Integrated Summary of Safety (Data Cut-off 30 June 1998)

D: Other Indications

Study No.	Principal Investigator (Number if multiple sites)	Country	Dates of Conduct	Status	Report Location in NDA (Vol. / Page No.)*
Controlled Studies in Cognition – Included in N999 Database					
N008	Frazer, Spokes	United Kingdom	12/89-4/91	Complete	405 / 93099
N010	Multiple (5)	Belgium	2/88-11/90	Complete	406 / 93321
N011	Multiple (6)	United Kingdom	4/88-4/90	Complete	407 / 93674
N012	Multiple (6)	United Kingdom	3/88-10/89	Complete	410 / 94747
N013	Multiple (5)	Belgium	1/88-3/90	Complete	412 / 95551
N014	Multiple (8)	France	11/88-6/90	Complete	416 / 96887
N022	Winblad	Sweden	1-6/90	Complete	420 / 98324
N023	Crook/Bahar	United States	10/88-8/89	Complete	420 / 98473
Controlled Studies in Cognition – Not Included in N999 Database					
N000	Dolce	Italy	1983	Complete	405 / 93071
N081	Dolce	Italy	1988	Complete	424 / 99596
Controlled Studies in Anxiety –Included in N999 Database					
N019	Multiple (120)**	United Kingdom	10/90-10/91	Complete	424 / 99642
N021	Salama	Belgium	4/90-2/91	Complete	433 / 103259
N041	Multiple (5)	Belgium	5-10/92	Complete	434 / 103760
N042 N122	Van Vlasselaer / Lemoine	Belgium France	8/93-8/94	Complete	435 / 104086
N043 N044 N045	Hugues** Linden Rouillon	United Kingdom Germany France	12/92-7/94	Complete	438 / 105154
Open Label Studies in Anxiety –Included in N999 Database					
N020	Godderis	Belgium	10/90-4/92	Complete	429 / 101608
Other – Included in N999 Database					
N099	Schoonbrood / Phillippart	Belgium	5-9/89	Complete	451 / 110063

* CRF tabulations and selected CRFs are provided electronically in NDA Sections 11 and 12, respectively.
** One investigational site, Dr. Brierley, was excluded due to questions about the patients included.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: November 18, 1999

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-035

SUBJECT: Recommendation for Action on NDA 21-035, for the use of Kepra (levetiracetam) in patients with partial seizures

On 2/1/99, UCB Pharma, Inc., submitted NDA 21-035 for the use of levetiracetam to treat partial seizures in adults with epilepsy. In support of the NDA, the sponsor submitted the results of 4 controlled trials, 3 of which were presented as demonstrating the effectiveness of levetiracetam. In addition, the NDA contains safety data from over 3000 subjects/patients who received at least one dose of levetiracetam.

The NDA has been reviewed by Dr. Joel Freiman of the Division (safety and efficacy review dated 11/18/99), Dr. Ohidul Siddiqui, Biometrics (11/9/99 statistical review of the effectiveness data), Dr. Hong Zhao, Office of Clinical Pharmacology and Biopharmaceutics (review dated 11/3/99), Dr. Jennifer Burris, Pharmacology (review dated 10/28/99), and Dr. Thomas Oliver, Chemistry (reviews dated 5/21/99, 9/28/99, and 11/17/99). All reviewers recommend that the application be approved.

In this memo, I will briefly review the effectiveness and safety data, other relevant issues, and offer the Division's recommendation for action on the NDA.

EFFECTIVENESS

The sponsor has submitted the results of 3 adequate and well controlled trials they believe support a finding of substantial evidence of effectiveness. A fourth trial (Study 052), although controlled, examined higher doses than the other 3, was apparently designed primarily to assess the tolerability of these higher doses, and was ostensibly not adequately powered to demonstrate effectiveness. I will mention this trial very briefly later. Below, I will briefly describe the 3 controlled trials the sponsor submits as providing substantial evidence of effectiveness.

STUDY 051

This was a randomized, double blind, placebo and fixed dose, 2 period counter-balanced cross-over, multi-center trial comparing the effectiveness of 2 doses of levetiracetam (1000 and 2000 mg/day, given as BID dosing) to placebo in patients with inadequately controlled partial seizures.

Eligible patients entered a 12 week prospective baseline period, during which they received stable doses of at least one and up to 2 anti-epileptic drugs (AED). Patients with

at least 4 partial seizures in each month of the baseline period were eligible to be randomized to treatment. After randomization, patients entered a 4 week Transition Phase, during which study drug was titrated to the assigned dose for Period 1. Treatment Period 1 lasted for 12 weeks, followed by Transition Phase 2 (4 weeks), followed by Treatment Period 2 (12 weeks). Patients were randomized into one of the following 6 sequences:

Placebo-Lev 1000 mg/day
Placebo-Lev 2000 mg/day
Lev 1000 mg/day-Placebo
Lev 1000 mg/day-Lev 2000 mg/day
Lev 2000 mg/day-Placebo
Lev 2000 mg/day-Lev 1000 mg/day

The primary outcome measure in this trial was the mean weekly frequency of partial seizures, based on seizure counts as recorded in patient diaries. Secondary measures included:

Responder rate – responder defined as a patient with at least a 50% decrease in the frequency of partial seizures compared to baseline

Incidence of Seizure free patients

Absolute and Percent reduction in partial seizure frequency compared to baseline

Response to Treatment-percent reduction of partial seizure frequency compared to baseline classified into 1 of 6 categories

The study was to be analyzed as a cross-over, but the protocol appeared to imply that an analysis of the first period data was also to be primary. The analysis of the primary outcome as a cross-over was to be an ANOVA of the log transformed mean weekly partial seizure frequency. The primary analysis of the first period, parallel group data was to be an ANCOVA of the log transformed mean weekly partial seizure frequency with the log transformed mean weekly partial seizure frequency at baseline as the covariate.

Results

A total of 324 patients were randomized at 62 centers in Europe. The following chart displays patient flow through the trial:

Sequence	Number Randomized
P-L1000	58
P-L2000	54
L1000-P	53
L1000-L2000	53
L2000-P	54
L2000-L1000	52

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Number randomized	Placebo	Lev 1000 mg/day	Lev 2000 mg/day
Period A	112	106	106
Period B	107	110	107
Completed Period A	97 (87%)	94 (89%)	87 (82%)
Entered Period B	88	94	96
Completed Period B	72	81	79
% Randomized who entered	82%	85%	90%
% Randomized who completed	67%	74%	74%
% Entered who completed	82%	86%	82%

The number of patients who completed the cross-over in each of the 6 sequences was not presented.

The following chart presents the results for the primary outcome measure, Mean Weekly Partial Seizure Frequency (taken from Dr. Siddiqui's Table 1.2, page 6). All results presented are based on data that do not include post-randomization data from the Transition Phases. Analyses have been performed that do include all post-randomization data; the results of these analyses conform to those displayed below.

Cross-over

	N	Mean Sz Freq	% Reduction over Placebo	P-value
Placebo	172	1.37		
Lev 1000	183	1.24	17%	<0.001
Lev 2000	175	1.22	19%	<0.001
First Period				
Placebo	106	1.40		
Lev 1000	101	1.28	16%	0.006
Lev 2000	95	1.31	18%	0.003

Secondary Outcomes

Cross-over

	N	% Reduction from Baseline	%>50% Reduction in Sz Frequency
Placebo	172	7.0	12
Lev 1000	183	23	26
Lev 2000	175	24	34
P-value			
1000 vs P		<0.001	0.004
2000 vs P		<0.001	0.001
2000 vs 1000		0.59	0.018
First period			
Placebo	106	6	10
Lev 1000	101	18	23
Lev 2000	95	27	32
P-value			
1000 vs P		0.006	0.019
2000 vs P		0.003	<0.001
2000 vs 1000		0.80	0.018

STUDY 132

This was multi-center, randomized, double blind, placebo and fixed dose response, parallel group trial in patients with inadequately controlled partial seizures.

Eligible patients who were on stable doses of between 1-2 concomitant AEDs were entered into a single blind placebo 12 week baseline phase. Patients with 12 partial

seizures, with at least 2 in each 4 week epoch of the baseline phase were eligible to be randomized to Placebo, Lev 1000 mg/day or Lev 3000 mg/day, given as BID dosing.

The first 6 weeks post-randomization consisted of a Titration Phase, followed by a 12 week Treatment phase, followed by an 8 week withdrawal phase.

The primary outcome measure was the Mean Weekly Partial Seizure Frequency. The primary analysis was to be an ANCOVA of the log transformed seizure frequency with the log transformed baseline partial seizure frequency as the covariate. The protocol called for a Bonferroni adjustment in the alpha level for multiple comparisons.

Secondary measures included Absolute and Percent Reduction in Seizure Frequency compared to baseline, responder rate, incidence of seizure free patients.

Results

A total of 294 patients were randomized at 41 centers in the United States. The following chart displays patient flow in the trial:

	Placebo	Lev 1000 m/d	Lev 3000 m/d
Randomized	95	98	101
Completed	89 (94%)	86 (88%)	93 (92%)
Included in ITT Analysis	93	94	98

All of the results presented below utilized data from the last 2 weeks of the Titration Phase and the Treatment Phase. Analyses were done which included all post-randomization data (including additional data accrued in the Titration Phase). While the results of these latter analyses are not presented, they are consistent with those presented.

The following displays the results of the analysis of the primary outcome measure, Mean Weekly Partial Seizure Frequency:

	Baseline	Mean on Tx	% Reduction vs Placebo	P-value
Placebo	1.26	1.23		
Lev 1000	1.56	1.28	21	<0.001
Lev 3000	1.38	1.03	28	<0.001

Secondary Measures

	% Reduction vs baseline	>50% Reduction vs baseline
Placebo	7	11
Lev 1000	33	33
Lev 3000	37	40
P-value		
Lev 1000 vs Pla	<0.001	<0.001
Lev 3000 vs Pla	<0.001	<0.001
Lev 3000 vs Lev 1000	0.194	0.196

STUDY 138

This was a randomized, double blind, parallel group, placebo controlled multi-center trial that examined the effects of Lev 3000 mg/day in patients with inadequately controlled partial seizures. The trial consisted of 2 phases; the first phase (to be described in more detail below) examined Lev in an adjunctive setting, followed by a Monotherapy phase. Because the monotherapy phase was not adequate by design to address the effectiveness of Lev as monotherapy (entrance into this phase was not randomized), the sponsor has not submitted it as evidence of effectiveness in monotherapy, and I will not discuss this phase further.

Eligible patients who were receiving one concomitant AED at a stable dose entered a 12 week prospective Baseline Phase. Patients who had at least 2 complex partial seizures in each 4 week epoch of the Baseline Phase were randomized to Lev 3000 mg/day or Placebo (in a 2:1 ratio) for a 12 week Treatment Phase.

Although the ultimate purpose of the study was to evaluate the effectiveness of Lev as Monotherapy, the protocol did contain a description of the primary outcome of Part 1 of the study, namely the adjunctive phase (the protocol seems to imply that the monotherapy and adjunctive portions were both "primary" parts of the study). The protocol specified primary outcome of the adjunctive portion of the trial was the Mean Weekly Partial Seizure Frequency, to be analyzed by an ANCOVA of the log transformed data, with the log transformed baseline weekly partial seizure frequency as the covariate.

Secondary measures included Responder Rate, Response to Treatment, Incidence of Seizure Free patients, and absolute and % reduction in seizure rate compared to baseline.

Results

A total of 286 patients were randomized at 47 centers in Europe. The following chart displays patient flow in the study:

	Placebo	Lev 3000 m/d
Randomized	105	181
Completed	90 (86%)	149 (82%)
Included in ITT analysis	102	171

All of the results presented below utilized data from only the Treatment Phase. Analyses were done which included all post-randomization data (including data from the Titration Phase). While the results of these latter analyses are not presented, they are consistent with those presented.

The following displays the results of the analysis of the primary outcome measure, Mean Weekly Partial Seizure Frequency:

	Baseline	Mean on Tx	% Reduction vs Placebo	P-value
Placebo	1.24	1.17		
Lev 3000	1.18	0.90	22	<0.001

Secondary Measures

	% Reduction vs baseline	>50% Reduction vs baseline	P-value
Placebo	7	17	
Lev 3000	40	42	
P-value	<0.001	<0.001	

STUDY 52

This was a randomized, double blind, placebo and fixed dose parallel group multi-center trial in patients with refractory epilepsy of any seizure type.

Patients with inadequately controlled epilepsy were randomized to receive placebo, Lev 2000 mg/day or Lev 4000 mg/day for 24 weeks. The primary outcome measure was the

Responder Rate, as previously defined, but including all seizure types. The study was not powered to demonstrate effectiveness. Patients were to be taking 1-3 concomitant AEDs, and have at least 4 seizures during the 24 weeks prior to the study.

Results

A total of 119 patients were randomized at 37 centers in Belgium and the UK. The following chart displays patient flow in the trial:

	Placebo	Lev 2000 m/d	Lev 4000 m/d
Randomized	39	42	38
Completed	29 (74%)	28 (66%)	29 (76%)
Included in ITT analysis	37	36	36

The following chart displays the results of the analyses of the primary outcome, Responder Rate:

	Placebo	Lev 2000 m/d	Lev 4000 m/d
	6/36 (16.7%)	14/34 (41.2%)	10/36 (27.8%)
P-Value (vs Pbo)		0.027	0.259

It is unclear from the reviews exactly which patients were included in this analysis (for example, the denominators here do not exactly correspond to the numbers presumably included in the ITT population). Other analyses that used only completers gave similar significance patterns.

While both doses showed a numerical superiority compared to placebo in decreasing seizure frequency (with Lev 2000 numerically superior to Lev 4000), the comparisons did not reach statistical significance (P=0.24-0.25).

SAFETY

The NDA contains well documented safety data for a total of 3340 subjects/patients, followed prospectively, who received at least one dose of levetiracetam. A total of 1388 unique adult patients with epilepsy received treatment with levetiracetam, with 769 in controlled trials.

The median duration of exposure among the 1388 patients with epilepsy was 344 days, with 971 unique epilepsy patients exposed for at least 6 months, and 674 unique patients

exposed for at least 1 year. Essentially all experience beyond 3 months was gained in epilepsy patients.

A total of 919 epilepsy patients received at least 1 day of dosing at greater than 2500 mg/day; a total of 540 epilepsy patients received daily doses of between 2500 mg and 3500 mg for at least 6 months (and 341 received these doses for at least 1 year). A total of 243 epilepsy patients received doses of between 3500 and 4500 mg/day for at least 6 months, with at least 177 receiving these doses for at least 1 year.

Deaths

As of 2/99, a total of 35 deaths occurred in the development cohort for whom reliable data is available. A total of 4 of these patients died in baseline portions of clinical trials; therefore, the subsequent discussion will apply to the remaining 31 deaths.

A total of 28 of these deaths occurred in patients being treated with LEV or within 30 days of discontinuing treatment; 3 occurred in placebo patients. The overall mortality for LEV patients was 11.4/1000 pt-yr., compared to 12.3/1000 pt-yr. for placebo treated patients. For epilepsy patients, the respective mortality was 9.3/1000 PYs and 13.1/1000 PYs (the corresponding rates in controlled epilepsy trials was 10.7 vs 13.9). For non-epilepsy patients, the overall LEV mortality was 42.9/1000 Pies (7 deaths) compared to 11/1000 PYs for the placebo patients (1 death).

In this latter non-epilepsy cohort, 3 of the LEV deaths clearly appeared to be related to advance cancer. Removing these patients from the numerator for the LEV mortality rate lowers the mortality to 24.5/1000 PYs for the LEV group. Examination of these deaths revealed one patient who suffered an MI (93 year old woman with history of cardiac valvular disease and pulmonary hypertension) and a suicide in a 45 year old woman. Other causes included CVA and the previously mentioned cancer patients.

Of the deaths in epilepsy patients, none appeared related to treatment, although there was one suicide (a 43 year old man who received 3000 mg/day for 128 days who was allegedly having marital and financial problems, but with no depression noted during the study); there were 9 deaths classified as Sudden Unexplained Death in Epilepsy (SUDEP). The SUDEP rate was 3.7/1000 PYs, essentially the same as for other recently approved AEDs.

Discontinuations

A total of 131/769 (17%) LEV patients and 61/439 (14%) of placebo patients discontinued treatment during controlled trials in patients with epilepsy. Of these, 86 (11% of the total) of the LEV patients discontinued due to an adverse event, compared to 35 (8% of the total) of the placebo patients.

In these controlled trials, the most common adverse event leading to discontinuation was Somnolence (3% of LEV vs 0.9% of Pbo patients). The next most common ADRs

resulting in discontinuation of LEV and which occurred at least twice as often as placebo were Headache (0.9%), Accidental Injury and Dizziness (each 0.5%), and Hostility, ataxia, emotional lability, insomnia, nervousness, personality disorder, and thinking abnormal, all 0.4%. One placebo patient discontinued due to severe mood swings and a confusional state which resolved the day after drug was discontinued. I will discuss these behavioral events in more detail later in the review. In addition to these events, a 47 year old woman with a history of situational depression who had received 3000 mg/day of LEV for 56 days developed an episode of "suicidal tendency" (see Dr. Freiman's review, page 48). Drug was tapered off starting 14 days later, but there is no additional follow-up data.

In the larger epilepsy cohort, there were 22 additional patients who discontinued LEV treatment secondary to behavioral abnormalities. In addition, Dr. Freiman describes (pages 50-51) 9 other patients in this cohort who discontinued secondary to laboratory abnormalities.

1) a 44 year old man with a baseline GGT of 731 IU/L who, after 577 days of treatment developed a GGT of 1827 IU/L, with associated AST of 78 IU/L, ALT 105 IU/L normal Bilirubin and alk phos of 378 IU/L. LEV was discontinued, and last values were: GGT 780, AST 49, ALT 73, Alk Phos 295.
2) A 52 year old male treated with LEV for 268 days with a GGT of 641, AST 121 (ULN 30), ALT 182, and Alk Phos 150 (ULN 128); bilirubin was 1.4 (ULN 1.0). LEV and Valproate were discontinued, with return of ALT, AST, Alk Phos, bilirubin to normal and GGT slightly elevated (179) 4 months after discontinuation.
3) A 37 year old woman who developed GGT 2XULN, AST 2XULN, and ALT <5XULN after 7 months of treatment, then GGT 5XULN, AST <6XULN, and ALT 12XULN one month later; bilirubin was never elevated. Drug discontinuation occurred about 6 weeks after this last lab assessment, after which levels began to return to normal (GGT and ALT still slightly elevated, but close to baseline values).
4) A 51 year old man with a history of alcohol abuse and elevated GGT at baseline had a persistently elevated GGT after more than 600 days on 4000 mg/day of LEV. Other labs are not reported.
5) A 53 year old woman had a WBC of 4200/L and neutrophils of 1790/L after 247 days of treatment. A CBC 2 months after drug discontinuation revealed a neutrophil count of 1940/L.
6) A 30 year old man with a glioma and history of intermittent eosinophilia developed an eosinophil count of 18.4% after 113 days of treatment (he was also receiving chemotherapy). The count was still elevated 2 weeks after drug discontinuation, but dropped to 7.7% after tumor resection.
7) A 57 year old woman had a WBC of 3100/L and neutrophil count of 1170/L after 15 days of treatment with 1000 mg/day. These resolved at 2 weeks after drug was discontinued.
8) A 47 year old man was hospitalized for seizures and developed rhabdomyolosis after 34 weeks of treatment. This led to acute renal failure from which he recovered.
9) A 40 year old woman who developed a rash (not described) after 6 months of treatment. The rash resolved after 6 months.

Adverse events leading to discontinuation in patients receiving LEV for other indications (cognition and anxiety) that occurred at least twice as often on LEV compared to placebo were somnolence (1.7%), nausea (1.2%), asthenia and depression (0.6%), and vertigo (0.4%).

Adverse Events

In controlled trials in epilepsy patients, the following adverse events occurred with a frequency of at least 3% in LEV treated patients and twice as frequently as in placebo patients (taken from Dr. Freiman's Table 53, page 53): Dizziness (8.8% vs 4.1%) and Nervousness (3.9% vs 1.8%).

The sponsor evaluated the dose relationship of adverse events in epilepsy controlled trials (Table 55, Dr. Freiman's page 55). There are no ADRs that follow a clear monotonically increasing relationship to dose, although there is a striking incidence of somnolence in patients receiving 4000 mg/day (17/38, or 45%).

In all epilepsy patients, the most common ADRs were accidental injury and headache (25%), infection (23%), asthenia, somnolence, and convulsion (22%). Other commonly occurring ADRs included dizziness (18%), pain (14.5%), pharyngitis (11.1%), and flu syndrome (10.1%) (See Dr. Freiman's table 56, page 55, for additional event incidences).

Serious Adverse Events

In controlled trials of patients with epilepsy, serious adverse events of interest were suicide attempt (0.5% vs 0 in pbo), personality disorder (0.4% vs 0 in pbo), and psychosis and somnolence (each 0.3% vs 0 in pbo).

Dr. Freiman has reviewed the narratives of all serious adverse events in this cohort. Of interest are 4 cases of suicide attempt; one was described earlier (patient withdrew from treatment), while the other 3 continued on treatment.

In all epilepsy patients, the only non-seizure related serious ADR that occurred at a frequency greater than 1% was accidental injury (4.2%). Other serious ADRs of interest included the behavioral symptoms noted earlier in the review (see Dr. Freiman's Table 59, page 58).

Serious ADRs occurred in 2.3% of non-epilepsy patients treated with LEV compared to 2.1% of Placebo treated patients. Of interest, one patient was treated for 2 days with 1000 mg/day when elevated bilirubin and Alk Phos were noted. Further details are not available, though apparently the patient continued to have fluctuating bilirubin and Alk Phos levels following discontinuation of LEV.

Laboratory Data

The sponsor evaluated lab data by assessing mean changes as well as examining the proportion of patients who had lab values outside of acceptable ranges. These latter values were referred to as Possibly Clinically Significant (PCS) values. The values used to classify these values as PCS were those previously endorsed by the division.

Liver

In controlled epilepsy trials, there were no important mean changes in LFTs for drug or placebo treated patients. There was an equal incidence (1.4%) of patients with a PCS value for LFTs (including AST, ALT, GGT, Alk Phos, or bilirubin) in LEV and Placebo treated patients.

Among all epilepsy patients, there was no increase in mean levels of LFTs.

A total of 9 patients had a PCS increased AST, 15 had a PCS increased ALT, 4 had a PCS elevated GGT, and 2 had a PCS elevated Alk Phos. There were 3 patients with a PCS elevated bilirubin; in 2 of these patients, the elevated bilirubin were isolated values (maximum of 2.6 mg/dl) while in the third patient, the increase was sustained (maximum level 2.3 mg/dl) while on treatment. Other than those patients described earlier under Discontinuations, none of these patients discontinued treatment, and none of them had elevated bilirubin in conjunction with any other LFT elevation.

Kidney

There were no increases in mean Creatinine, BUN, or creatinine clearance in LEV or Pbo treated patients in epilepsy controlled trials. In addition, 0.7% of LEV treated patients and 0.9% of Placebo treated patients had a PCS BUN in controlled trials, while there were no PCS abnormal creatinine values in either treatment group.

Among all epilepsy patients, there were no important mean changes in BUN or creatinine, nor were there any important mean changes in the mean creatinine clearance in the 464 patients in whom this was assessed.

There was 1 patient with an isolated PCS elevated creatinine (no further information is available, though the patient did not discontinue treatment), and 17 patients with a PCS elevated BUN. Of these 17, 4 were elevated at the end of treatment (these patients did not discontinue due to this finding), and in the other 13, the BUN had returned to baseline levels on treatment.

Electrolytes

There were no meaningful mean changes in serum sodium or potassium in controlled epilepsy studies. In these controlled trials, 0.2% of LEV treated patients and 0% of

Placebo treated patients had a PCS decrease in serum potassium; 7.2% of LEV treated patients and 8.2% of placebo patients had a PCS elevation in serum potassium.

Among all epilepsy patients, there were no important mean changes in serum Na or K, and there were 7 patients (not in controlled trials) who had a PCS decrease in K, and 148 patients with a PCS increased serum K.

Hematology

Comparisons of mean changes between LEV and placebo treated patients in epilepsy controlled trials of various hematologic parameters reached statistical significance, as described below:

	Mean change from baseline	
	Levetiracetam	Placebo
RBC ($X10^9$/L)	-0.04	-0.01
Hemoglobin (g/dL)	-0.1	-0.01
Hematocrit (%)	-0.33	+0.05

In controlled trials, 4.9% of LEV treated patients and 3.4% of Placebo treated patients had a PCS decreased hematocrit. A total of 3% of LEV patients and 1.8% of placebo patients had a PCS decreased WBC, and 2.1% of LEV patients and 1.4% of placebo patients had a PCS neutrophil count. A total of 0.4% of LEV patients and 0.2% of Placebo patients had a PCS decreased hemoglobin.

The vast majority of the PCS values of hematocrit were minor and returned toward or to baseline values with continued treatment (see Dr. Freiman's Table 69, page 68). The greatest drop occurred in a patient whose baseline Hct was 53, which dropped to a low of 32, and which was 35 at her final visit. Other than those patients discussed under Discontinuations, none of these patients discontinued due to Hct abnormalities.

In all epilepsy patients, there were 1.8% of patients with a PCS decreased Hemoglobin, and 8.1% of patients had a PCS decreased Hct.

In epilepsy controlled trials, 4.5% of LEV patients and 3.2% of Placebo patients had a PCS decreased WBC, neutrophil, or lymphocyte count. A total of 2% of LEV patients and 3.8% of placebo patients had a PCS increase in eosinophils.

A total of 2.1% of LEV patients compared to 1.4% of placebo patients had a PCS decreased neutrophil count. Of these 16 LEV patients with a PCS decreased neutrophil count, 15 no longer had a PCS value at the end of their treatment (as can be seen in Dr. Freiman's Table 70, page 69, some patients who had extremely low neutrophil counts were continued on drug with a return of the neutrophil count to reasonable, though often low, levels).

Among all epilepsy patients, 19 had neutrophil counts below .75 x 10^9/L. Of the 14 not in controlled trials, 13 had final values that no longer met the criteria for PCS. There were 4 patients in non-epilepsy studies who had neutrophil counts below .75 x 10^9/L. Of these 4, 2 had final values of .6 X 10^9/L after 28 days of treatment, with no additional follow-up (baseline values in these 2 patients were >4 x 10^9/L). One patient had a neutrophil count of .17 x 10^9/L, which persisted for 2 weeks after drug was discontinued, and the fourth patient had a neutrophil count of .34 x 10^9/L which returned to baseline levels 2 weeks after treatment discontinuation.

There were no important differences between LEV and placebo patients in platelet counts in patients with epilepsy. Of the few epilepsy patients who experienced a low platelet count, these counts rose while on treatment. One non-epilepsy patient had a final platelet count of 34 x 10^9/L after 2 weeks of treatment; this was the last value reported (baseline value was 305 x 10^9/L).

Vital Signs

There were no important mean changes in mean systolic or diastolic blood pressure, pulse, or body weight in controlled epilepsy studies.

The incidence of PCS changes in systolic blood pressure was small (<1%) in both treatment groups and not different between the groups. A total of 0.4% of LEV patients and 0.2% of Placebo patients met criteria for a PCS decrease in diastolic pressure (the lowest recorded diastolic pressure was 50 mm Hg).

In all epilepsy patients, 1.7% and 1.4% of patients met criteria for PCS decreased and increased systolic pressure, respectively, and the corresponding figures for diastolic pressure were 1.6% and 1.5%.

There were no clinically important changes in pulse, although there were patients (N=12 for all epilepsy patients) with sinus bradycardia.

In controlled epilepsy trials, 6.2% of LEV patients and 5.0% of Placebo patients had a PCS increase in weight. The corresponding figures for decreased weight were 5.4% and 3.9%.

EKG

As can be seen in Dr. Freiman's Table 72 (page 73) there are no significant differences between LEV and placebo treated patients with regard to abnormal EKG events. As is also seen in his Table 73 (page 74) there were no important between group differences in EKG parameters (PR interval, QRS interval, QTc interval, and Heart Rate).

CNS Events

Somnolence

In controlled epilepsy trials, 14.8% of LEV patients and 8.4% of placebo patients reported somnolence, and 14.7% of LEV patients and 9/1% of placebo patients reported asthenia.

Coordination Difficulties

A total of 3.4% of LEV patients and 1.6% of placebo patients reported coordination abnormalities (consisting of abnormal gait, ataxia, cerebellar syndrome, and incoordination) in controlled epilepsy studies.

Cognitive Effects

The sponsor grouped the COSTART terms amnesia, confusion, and thinking abnormal to calculate that 3.6% and 2.7% of LEV and placebo patients, respectively, had cognitive effects in controlled epilepsy trials. In all epilepsy patients, about 10% of patients reported cognitive symptoms.

Behavioral Events

The sponsor grouped various COSTART terms into 4 Psychiatric Adverse Events categories: Psychotic symptoms, Nonpsychotic/behavioral symptoms, Auto-aggressive behavior (intentional overdose and suicide attempt), and Sleep disorders (see Dr. Freiman's review, page 78, for the specific terms subsumed under these 4 headings).

In controlled epilepsy studies, 0.7% of LEV patients and 0.3% of Placebo patients experienced psychotic symptoms, 13.5% of LEV patients and 6% of placebo patients experienced nonpsychotic/behavioral symptoms, 0.4% of LEV patients and 0% of Placebo patients experienced auto-aggressive symptoms, and 3.6% of LEV patients and 2.8% of placebo patients experienced sleep disorders. In trials of Cognition and Anxiety, drug-placebo differences for these symptoms were minimal. In the controlled epilepsy studies, 1.7% of patients discontinued due to nonpsychotic/behavioral symptoms, compared to 0.2% (1 patient) of placebo patients.

COMMENTS

The sponsor has submitted the results of 3 adequate and well controlled trials which, taken together, provide substantial evidence of effectiveness of levetiracetam as adjunctive treatment for partial onset seizures in adults with epilepsy. In addition, experience in over 3000 patients, and in over 1300 patients with epilepsy, establishes that

levetiracetam can be considered to be safe in use with appropriate labeling. A few issues require comment.

The sponsor has performed studies that examine doses of 1000, 2000, and 3000 mg/day in patients with partial onset seizures; all doses have been shown to be effective. One trial included 1000 and 2000 mg/day groups, one examined 1000 and 3000 mg/day, and one examined only 3000 mg/day. In the first trial, there was extremely minor numerical superiority of the 2000 mg/day group compared to the 1000 mg/day group, but no statistical significance, on the primary outcome measure. Of the 2 secondary outcome measures, numerical (but not statistical) superiority of the 2000 mg/day group compared to the 1000 mg/day group was seen on one, but a nominally statistically significant advantage of the 2000 mg/day group compared to the 1000 mg/day group was seen on the other.

In the second trial, minor numerical superiority of the 3000 mg/day group compared to the 1000 mg/day group was seen on the primary and secondary outcomes, but no statistical superiority was noted.

Given this pattern of dose response, I believe that labeling should recommend that patients should be started at the lowest effective dose (1000 mg/day) with the maximum recommended daily dose being 3000 mg/day. A small study examined the effects of a daily dose of 4000 mg/day, but there is no reliable evidence that this dose confers any additional benefit above that associated with the lower doses. Further, the experience at this high dose is limited, and a marked increased incidence of somnolence (45%) was seen at this dose.

The sponsor has proposed that the drug be approved for patients with partial onset seizures, with and without generalization. While this is an accurate description of the population studied, the division has consistently taken the position that such language implies an effect on the process of secondary generalization, in addition to the primary effect on reducing the frequency of partial seizures. Given our view, we have not permitted sponsors to include language like that proposed by this sponsor unless the results of an analysis specifically designed to address the question of the drug's effect on secondary generalization supports such a claim. We have proposed, for example, that sponsors perform a specific conditional analysis to address this question. This sponsor, however, has not presented the results of any analysis specifically designed to address this question (although the results of some analyses are described in their draft label). For this reason, they may not be permitted to include language that implies that levetiracetam has an effect on seizure generalization.

There are no safety concerns that would prevent the NDA from being approved. Minor, usually transient changes were seen in hematologic parameters, and no important consistent changes were seen in liver function tests, kidney function tests, EKG, or vital signs. Several patients experienced potentially serious events (including one patient with elevated LFTs and slightly elevated bilirubin), but there were no systematic important laboratory abnormalities noted.

Perhaps the most striking adverse events seen were CNS events, including somnolence, fatigue, cognitive impairments, and, most interestingly, behavioral events, including hostility, agitation, irritability, and other events. A number of patients attempted suicide (most had complicated histories); one was successful. Nonetheless, none of these (or related) events was unacceptably frequent or severe, in my view, to preclude approval.

Levetiracetam appears to have no important kinetic interactions with the major AEDs, which is both unusual and desirable for an AED.

As Dr. Fitzgerald notes in her memo of 11/10/99, the mouse carcinogenicity study has been found to be unacceptable by the CAC because a maximally tolerated dose was not reached. She recommends that the sponsor commit to performing a repeat mouse study in Phase 4, and I agree. I also agree that the study can be performed after approval of the NDA because all available data (genetox, mutagenicity screens, rat carcinogenicity study) suggest that the mouse study is likely to be negative, and uncontrolled epilepsy is a serious condition for which for which there is a need for additional therapies.

There are several patients for whom additional follow-up information needs to be obtained (e.g., several patients whose last recorded lab values were abnormal). Assuming we can get the sponsor to supply this information (or learn from them that the information is unavailable) in the next several days, I believe that it will be possible for the Agency to issue an Approval letter before the user fee due date of 12/1/99. Outstanding issues that must be resolved prior to that date include the firm's agreement to 1) adopt the dissolution specifications proposed by OCPB, 2) commit to a Phase 4 requirement to repeat the mouse carcinogenicity study, and 3) agree to adopt draft labeling. The sponsor has already agreed to the first 2, and we will negotiate labeling with them in the interim period before the due date. Importantly, the safety update, normally requested in an Approvable letter, would contain, in this case, a maximum of about 400 patient-years of additional exposure (serious adverse event and death data have been received up to 2/99 in the NDA). I believe, given the data we have in hand, that the application can be Approved without this minor additional increment of data, especially given that the company will be obliged to submit such an update within 3 months of approval.

APPEARS THIS WAY
ON ORIGINAL

/S/

Russell Katz, M.D.

APPEARS THIS WAY
ON ORIGINAL

Cc:
NDA 21-035
HFD-120
HFD-120/Katz/Freiman/Fitzgerald/Burris/Oliver/Guzewska/Malandrucco