

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-505

MEDICAL REVIEW

Review and Evaluation of Clinical Data

NDA (Serial Number)	21505 N(AZ)
Sponsor:	UCB Pharma Inc.
Drug:	Keppra
Proposed Indication:	
Material Submitted:	Response to Approvable
Correspondence Date:	5/21/03
Date Received / Agency:	5/22/03
Date Review Completed	7/10/03
Reviewer:	Norman Hershkowitz MD, PhD

1. Introduction/Background

This submission is a response to an approvable letter (4/17/03) to an NDA supplement submitted on 6/19/02 for a new oral solution form of Keppra. Keppra is presently available in tablet form. The Sponsor was asked to address the following issues regarding in the approvable letter: Concern for Medication dispensing errors, Labeling revisions (including the PPI), Clinical issue regarding abnormal Urinalysis, minor CMC issues. The Sponsor was also asked to provide any promotional material to this division as well as DDMAC. The Sponsors response to each issue will be discussed in the following sections.

2. Medication Errors

2.1 DNDP's concern regarding medication errors

The division, under the advisement of DMETS, was aware of several dispensing errors involving confusion between Keppra and Kaletra, a co-formulation antiretroviral treatment. None of these errors actually resulted in the administration of the wrong medication as they became recognized early. However, the concern was that with the new formulation that errors may increase in likelihood because of the resulting potential similarity of dosing instructions: e.g. 5 ml po BID. The Sponsor was requested, as a first step, to consider the following actions:

- Consider using a highlighted area or font style to emphasize the letters in the middle of the name that differ from Kaletra.
- Consider a "Dear Healthcare Practitioner" letter to alert practitioners to the potential for errors between Keppra and Kaletra.
- Alert patients to the potential confusion by directly addressing the problem in the Patient Package Insert (PPI).

2.2 Sponsors Response

The Sponsor has agreed to such changes. They note that they will be monitoring for additional errors and, if needed, they will reevaluate their risk management activities. Also noted is the fact that they were not aware of such errors. They recommend that Abbott Laboratories should also initiate a similar program. The following sections outline the actions taken by the Sponsor.

2.2.1 Artwork changes to package

The Sponsor plans to change the block letters to the Keppra logo used to identify Keppra on all trade containers and samples. This will differentiate Keppra from the package artwork for Kaletra that consists of block lettering. Examples of these changes are presented in Appendix A. This plan will be launched for the oral solution upon approval. The plan will be launched for the tablets within 180 days after approval.

While the Sponsor does not follow the exact recommendations by this division the change does help differentiate the two actual products so that one won't be inadvertently mistaken for the other. Rather than the middle of the name it differentiates the last part of the name ("eppra"). This is helpful and should be adequate.

2.2.2 "Dear Healthcare Practitioner" letter

The Sponsor has agreed to send such letters to pharmacist and physicians. These lists of health practitioners will come from lists of physicians who are currently visited by UCB sales representatives and pharmacists under the Pharm Alert program. These letters will be distributed at the time of the launch of the oral solution. Copies of these are contained in Appendix B.

The letter to practitioners alerts them of this problem and describes the drugs and risks of accidental substitution. The physicians letter discusses the importance of correctly communicating the prescription to the pharmacist. It also advises the physician to include the indication in the prescription, and recommends that the physician asks the patient to check medications they receive. The letter to the pharmacist advises them to obtain two independent checks in the dispensing process. It also recommends that the pharmacist opens the prescription bottle in the presence of the patient and reminds them to provide the patient with the PPI.

These actions appear adequate. This reviewer would suggest that the Sponsor use more expansive physician target for lists of mailing. It should include lists of Neurologists, primary care practitioners and Internists.

2.2.3 Information in the Patient Package Insert

UCB's revision to the PPI is noted as follows:

Before taking your medicine, make sure you have received the correct medicine. Compare the name above with the name on your bottle and the appearance of your medicine with the description provided below. Contact your pharmacist immediately if you believe a dispensing error .

Included in the PPI to assist the patients in this confirmation is the logo for Keppra as well as the description of all the formulations. This includes the color and shape as well as the flavor for the solution.

These changes appear adequate.

2.2.4 Additional Actions by the Sponsor

UCB noted that they would also provide information alerting both practitioners and patients to this potential medication error and add helpful suggestions on their website (www.keppra.com). This will be done within 6 months of launching the new formulation. The appropriate information will be submitted to DDMAC.

UCB will monitor for any additional cases of dispensing which will be reported in an expedited fashion. If such cases continue to occur The Sponsor will perform a reassessment of the present risk management program. They may wish to use that souci of information.

3. Clinical Issue

3.1 The Divisions concern regarding abnormal urinalysis

Examination of cumulative urinalysis by this reviewer for patients exposed to ≥ 6 month in uncontrolled extension studies revealed a high percent of abnormal results. The incidence of numbers of patients who exhibited "possibly clinically significant" abnormal results are presented in the table below:

Parameter		Total (> 6 mo.)
Glucose	N	1020
	High	16 (1.6%)
Protein	N	1021
	High	85 (8.3%)
RBCs	N	1005
	High	246 (24.5%)
WBCs	N	888
	High	228 (25.7%)

The incidence of abnormalities in protein RBC and WBC values appeared rather high to this reviewer. In my review I noted that because these values represent cumulative results for an extended time period (median exposure of 2 ½ years) and they lacked placebo comparison that the data was difficult to interpret. Unfortunately information or comparison to the original placebo controlled trials were not included in the prior submission. Such information was also unavailable in the present labeling or this division's previous review NDA medical review. Moreover the issue remained, even if such effects were not observed after short-term exposure, these observations might indicate a time delayed effect of the drug. Data was not adequately presented to examine for this. The Sponsor was therefore asked to investigate the cause of these abnormalities.

3.2 Sponsors Response

The Sponsor presents an argument for each separate class of abnormality (RBCs, WBCs and protein) based upon a similar strategy. Their prime contention is that, for the most part, these observations represent an accumulation of isolated and transient artifacts resulting from the method of sample collection with little clinical significance.

First they note that all samples were not collected as a "clean catch." Thus, some degree of contamination may be expected.

The sponsor points out that the data from placebo controlled trials indicate no difference between placebo and drug treated groups. These data are presented in the tables below. Note that the numbers, and percents, of "Possibly Clinically Significant Values" (PCS) are presented for all patients and are also broken down by sexes. The data is not only presented in terms of patients but also in terms of samples collected. The first thing to note is the fact that the incidence of PCS values in all groups were similar between patients in placebo and drug treated group.

Off note also is that the incidence, in terms of percent of PCS values for protein in patients on drug and placebo (6.9% and 7.3%, respectively) is rather close to the values observed for patients in open label studies (8.3%).

Table 2:1 : Number of Patients and Samples (%) with at Least One 2+ / 3+ Urine RBCs: Adequate and Well-Controlled Double Blind Studies in Patients with Epilepsy^(a)

	Levetiracetam n / N (%) ^(b)	Placebo n / N (%) ^(b)
Number of Patients	N=627	N=351
All patients	59 / 627 (9.4%)	35 / 351 (10.0%)
Males	8 / 335 (2.4%)	4 / 174 (2.3%)
Females < 50	48 / 250 (19.2%)	29 / 155 (18.7%)
Females ≥ 50	3 / 42 (7.1%)	2 / 22 (9.1%)
Number of Samples	N=2600	N=1336
All urine samples	89 / 2600 (3.4%)	47 / 1336 (3.5%)
Males	15 / 1439 (1.0%)	7 / 677 (1.0%)
Females < 50	70 / 995 (7.0%)	38 / 574 (6.6%)
Females ≥ 50	4 / 166 (2.4%)	2 / 85 (2.4%)

^(a) Attachment 3:3 (Additional Analyses on Urine PCS Values): Table 2:2 (by subject) and Table 1.2 (by sample) (Vol. 1, pg. 115)

^(b) n = Number of Subjects with at least one PCS (Possibly Clinically Significant) Value (or number of values)
 N = Number of Subjects with at least one RBC Value (or number of values)

Table 2:3 : Number of Patients and Urine Samples (%) with at Least One 2+ / 3+ Urine WBCs: Adequate and Well Controlled Double Blind Studies in Epilepsy^(a)

	Levetiracetam n / N (%) ^(b)	Placebo n / N (%) ^(b)
Number of Patients	N=483	N=280
All patients	69 / 483 (14.3%)	40 / 280 (14.3%)
Males	18 / 245 (7.3%)	10 / 132 (7.6%)
Females	51 / 238 (21.4%)	30 / 148 (20.3%)
Number of Values	N=1558	N=806
All urine samples	103 / 1558 (6.6%)	55 / 806 (6.8%)
Males	23 / 885 (2.6%)	12 / 397 (3.0%)
Females	80 / 673 (11.9%)	43 / 409 (10.5%)

^(a) Attachment 3:3 (Additional Analyses on Urine PCS Values): Table 2:2 (by subject) and Table 1.2 (by sample) (Vol. 1, pg. 115)

^(b) n = Number of Subjects with at least one PCS Value (or number of values)
 N = Number of Subjects with at least one WBC Value (or number of values)

Table 2:5 Number of Patients and Urine Samples (%) with at Least One 2+ / 3+ Urine Protein: Adequate and Well-Controlled Double Blind Studies in Epilepsy^(a)

	Levetiracetam n / N (%)^(b)	Placebo n / N (%)^(b)
Number of Patients	N=721	N=416
All patients	50/721 (6.9%)	31/416 (7.5%)
Males	22 / 395 (5.6%)	18 / 211 (8.5%)
Females	28 / 326 (8.6%)	13 / 205 (6.3%)
Number of Values	N=3009	N=1550
All urine samples	88/3009 (2.9%)	44/1550 (2.8%)
Males	36/1658 (2.2%)	21/797 (2.6%)
Females	52 / 1351 (3.8%)	23 / 753 (3.1%)

^(a) Attachment 3:3 (Additional Analyses on Urine PCS Values): Table 2:2 (by subject) and Table 1.2 (by sample) (Vol. 1, pg. 115)

^(b) n = Number of Subjects with at least one PCS Value (or number of values)
 N = Number of Subjects with at least one protein value (or number of values)

The Sponsor presents data from the open label long-term extension trials for RBCs and WBCs in the two tables below. These are grouped in a similar fashion as those above. As noted above the Sponsor argues that the high frequency of abnormalities largely results from spurious contamination of the urine samples because of the technique of sample collection. They support this by pointing out that although patients frequency of the elevation of WBC and RBC counts were high compared to drug and placebo groups in the pivotal trials, the frequency of abnormal samples were similar. To further support this conclusion the Sponsor points out that if contamination was a significant factor it may be expected to appear at a higher rate in women because of vaginal and labial secretion contamination as well as menstrual contamination. This is born out from the data presented in all tables; i.e. pivotal and long term trial data on RBC and WBC data. Thus in all cases a greater number RBC and WBC indices were found to be abnormal in women then in men. Moreover consistent with the issue of menstrual contamination, women below 50 years of age exhibited a higher incidence of abnormal PCS values for RBCs then that observed in older women or men. All the above observations would be consistent with the occurrence of such transient sporadic contamination.

Table 2:2 Number of Patients and Urine Samples (%) with at Least One 2+ / 3+ Urine RBCs: Long-Term Exposure (≥ 6 months)^(a)

	Levetiracetam n / N (%) ^(b)
Number of Patients	N=1005
All patients	246 / 1005 (24.5%)
Treatment-emergent	215 / 1005 (21.4%)
Males	37 / 559 (6.6%)
Females < 50	194 / 381 (50.9%)
Females ≥ 50	15 / 65 (23.1%)
Number of Samples	N=14,629
All urine samples	570 / 14629 (3.9%)
Males	80 / 8337 (1.0%)
Females < 50	455 / 5350 (8.5%)
Females ≥ 50	35 / 942 (3.7%)

^(a) Attachment 3:3 (Additional Analyses on Urine PCS Values): Table 2:1 (by subject) and Table 1:1 (by sample) (Vol. 1, pg. 115) and Attachment 3:4 Listing 18:6:1 KEPPRA Oral Solution NDA (21-505, ISS, Section 8, Volume N159, Pages 45255 – 45273) of levetiracetam treated patients with urine RBC PCSA (Vol. 1, pg. 185).

^(b) n = Number of Subjects with at least one PCS Value (or number of values)
 N = Number of Subjects with at least one RBC value (or number of values)

Table 2:4 Number of Patients and Urine Samples (%) with at Least One 2+ / 3+ Urine WBCs: Long-Term Exposure (≥ 6 months)^(a)

	Levetiracetam n / N (%) ^(b)
Number of Patients	N=888
All patients	228 / 888 (25.7%)
Treatment-emergent	196 / 888 (22.1%)
Males	60 / 472 (12.7%)
Females	168 / 416 (40.4%)
Number of Values	N=6552
All urine samples	519 / 6552 (7.9%)
Males	116 / 3770 (3.1%)
Females	403 / 2782 (14.5%)

^(a) Attachment 3:3 (Additional Analyses on Urine PCS Values): Table 2:1 (by subject) and Table 1:1 (by sample) (Vol. 1, pg. 115); a by patient listing is provided in Attachment 3:5 Listing 18:6:1 of KEPPRA Oral Solution NDA (21-505, ISS, Section 8, Volume 159, pages 45274 – 45291) (Vol. 1, pg. 205)

^(b) n = Number of Subjects with at least one PCS Value (or number of values)
 N = Number of Subjects with at least one WBC value (or number of values)

The Sponsor also provides a series of tables that breaks down incidence of abnormal PCS values according to time intervals of exposure to explore alterations in risk over time.

Examination of the tables for protein (tables not shown) presented for long term extended studies reveals no increase in risk with increase exposure, indeed if anything there was a slight reduction.

The table below presents information on RBC and WBC data for all patents studied in the long-term extension trails. Examination of this table suggests no apparent change in the percent of patients or samples exhibiting abnormal values for RBCs with increased duration of exposure. Moreover, the percent of PCS values for samples and patients do not appear different from those in the placebo or drug groups from the pivotal trials (see previous table 2:1). There, however, may such a tendency for increased incidence of PCS over time with WBCs. The Sponsor, however, states that the proportions are "constant across time intervals." Some of these values are greater than that observed for samples and in the placebo or drug groups from the pivotal trials (see previous table 2:3).

Percent PCS values for urine WBCs and RBCs in patients and samples observed in long term extended trial for all patients studied during specific time intervals of exposure

Time Interval	RBCs				WBCs			
	samples		patients		samples		patients	
	n	%	n	%	n	%	n	%
1d-6m	4508	3.4	947	10.9	1925	6.6	627	13.4
6m-1y	1929	4.8	842	9.3	839	5.1	435	8.0
1y-2y	2738	3.9	777	10.0	1428	8.5	548	15.9
2y-3y	2023	4.0	555	11.4	906	10.0	324	19.8
3y-4y	1591	4.2	426	11.0	758	6.2	247	13.8
4y-5y	1145	4.5	345	11.9	561	11.2	213	18.8
>5y	685	2.9	160	10.6	132	18.9	75	24.0

To further investigate this difference the reviewer constructed the table below that divides groups up according to sex. As is apparent while such a time dependency is not apparent for males there may be a small signal in females. This is apparent when broken down by patient or sample.

Percent PCS values for urine WBCs in patients and samples observed in long term extended trial broken down by sex

Time Interval	WBCs Males				WBCs females			
	samples		patients		samples		patients	
	n	%	n	%	n	%	n	%
1d-6m	1128	3.8	326	8.3	797	10.7	301	18.9
6m-1y	420	1.9	210	2.9	419	8.4	225	12.9
1y-2y	778	3.5	291	6.9	650	14.6	257	26.1
2y-3y	546	2.9	173	6.9	360	20.8	151	34.4
3y-4y	466	1.7	139	5.8	292	13.4	108	24.1
4y-5y	361	3.0	122	5.7	200	26.0	91	36.3
>5y	71	4.2	42	7.1	22	36.1	33	45.5

The male values are very close to those observed in the pivotal trials (table 2:3). Women receiving placebo in the pivotal trial control group exhibited a WBC PCS incidence by patient of 20.3% and by sample of 10.5% (see table 2:3). Comparison of this percent by sample reveals 3 time interval values elevated in comparison to the placebo group placebo treated patient in the pivotal trials (2-3 years, 4-5 years and >5 years). Because the number of patients from which interval values for >5 years was obtained is rather small the high values observed here may be questioned. This, however, leaves two abnormal intervals, 2-3 years and 4-5 years. This reviewer would be hard pressed to consider this a trend.

Pertinent to these abnormalities the Sponsor note that review of laboratory analysis 'did not reveal significant levels of urinary casts.'

The Sponsor subsequently discusses PCS values that were considered by each investigator as "clinically significant."

The PCS values were thought to be "clinically significant" in 5 (or 0.5%) patients. Two patients had UTIs, one had proteinuria and bacteria noted as an adverse event, RBCs and WBCs were elevated in another.

For those patients who experienced RBC PCS values, 15 patients (1.5%) were thought to be "clinically significant." Ten of these were noted to have urinary tract infections. Three of the patients were thought to have other unrelated adverse events that were described by the following terms in the different patients: 1) interstitial nephritis, bilateral renal cysts, glomerular disease; 2)-decrease creatine clearance; 3) hematuria with possibly early menopause. Most of these patients also exhibited WBCs in their urine. Hematuria was associated with excessive coumadin treatment in one other patient and was attributed to a renal cyst in another. Four additional patients had hematuria reported as an adverse event.

The presence of PCS values for WBCs in urine was judged to be "clinically significant" in 29 (or 3.3%) of patients. All but 8 of these were attributed to UTIs or yeast infections. Of these 8, one was thought to have a mild interstitial nephritis, bilateral renal cysts, glomerular disease (presumably the same patients as that noted above) and one had an earlier episode of UTI and abuminuria

and proteinuria with a yeast infection." There were no adverse events associated with the remaining 6 patients.

The prior data submitted and reviewed safety data contained in the last labeling supplement did not suggest any new trends in alterations of creatinine. There were two cases of renal pathology reported as a serious event. One patient was a 22 year old male who was hospitalized for anuria and renal insufficiency. While undergoing dialysis his "renal function" "normalized." A biopsy suggested glomerulonephritis of toxic origin. This was attributed to the topiramate that he was also on. There, however is nothing in topiramate's labeling to indicate an association with glomerulonephritis. There was another patient with renal failure who had an extensive use of anti-inflammatory agents. A nephrology consult believed this resulted from drug toxicity, presumably secondary to anti-inflammatory use. The patient improved without dialysis. There were also two pediatric reports of kidney stones.

In summary, it appears abnormal values reported for protein was not different from that reported for patients receiving placebo in pivotal trials. Although, when broken down by patient, the percent of grouped PCS values for RBCs and WBCs were higher in long term extension studies than patients exposed to placebo and drug in pivotal trials, they were similar when broken down by sample. This along with the fact that that these differences were most marked in young women supports the Sponsors contention that these abnormalities resulted from sample contamination. When long-term extension data is broken down by time interval, except perhaps for WBC, no apparent temporal trend can be appreciated. In the case of WBCs, the trend was not completely consistent. No definitive statement can be made in this regard. Examination of serious adverse events do not, at the present time suggest a trend, toward renal pathology. In conclusion, the Sponsor makes a reasonable argument that no action is necessary at the present time, however they should practice increase vigilance regarding renal pathology.

4. Labeling

Included in this submission was an additional revision to the labeling and the PPI. This division had previously made a small number of changes in the labeling and more extensive changes in the PPI. The sponsor has resubmitted additional labeling PI and PPI changes in the form of "track changes" using the FDA proposed package insert draft labeling included in the original approvable letter (4/17/03) as a base document. These documents are only available in paper and not electronic format

4.1 Package Insert

4.1.1 Chemistry Issues

Two changes have been made by the Sponsor that is presently under review by chemistry. They are both in the DESCRIPTION section of the PI. These changes include the following change based upon a statement added as a result of an FDA correspondence of March 14, 2003.

Levetiracetam is a white to off-white crystalline powder with a faint odor and a bitter taste. It is very soluble in water (104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane. (Solubility limits are expressed as g/100 mL solvent.)

The following change was made because of the discontinuation of a coloring agent to one of the tablets.

The individual tablets contain the following coloring agents:

250 mg tablets: FD&C Blue No. 2,

500 mg tablets: yellow iron oxide,

750 mg tablets: FD&C Blue No. 2, FD&C Yellow No. 6 and red iron oxide.

Chemistry will comment on these changes.

4.1.2 Stylistic, grammatical and spelling changes

A number of stylistic, grammatical and spelling changes can be found throughout the submitted PI. All such changes are acceptable. The reviewer should however note some inconsistencies in the documentation of these changes.

First the following changes were made in the precautions section:

Keppra (1500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers.

According to the table describing this change the ~~_____~~ was removed. This was done.

In other cases where an underscore is noted to have been added, none are seen in the track changes. Moreover, spaces noted to be deleted according to the table could not be appreciated in the track change version provided by the Sponsor. These changes will be corrected in this division's construction of the final labeling.

The sponsor should check these minor issues.

4.1.3 Changes to the Overdosage section

The following changes were made to this section.

Signs, Symptoms And Laboratory Findings Of Acute Overdosage In Humans

The highest known dose of Keppra received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse events in the few known cases of overdose in clinical trials. Cases of somnolence, agitation aggression, depressed level of consciousness, respiratory depression and coma were observed with Keppra overdoses in postmarketing use.

These changes are base upon a previous labeling supplement (CBE) that was submitted on January 28 2003. The division previously notified that the Sponsor that they agreed with the CBE but a formal review had not been written. What follows is that formal review.

The Sponsor has submitted a review of 10 postmarketing overdose cases. Four of these involved overdose with Keppra alone. Six cases are complicated by simultaneous overdose with other anticonvulsants. All cases are summarized in the table below.

Table 1:6 Cases of Overdose

Case ID	Medication	Dose	Symptoms	Outcome
1006085	Keppra	40g	coma, sopor, somnolence	recovered
	citalopram HBr	10 tablets (dose unknown)		
	alprazolam	unknown		
2000549	Keppra	30g	coma, respiratory depression	recovered
1002719	Keppra	30g (15g/day for 2 consecutive days)	somnolence, hyponatraemia, leukopenia, anaemia, thrombocytopenia	unknown
	carbamazepine	22 tablets (dose unknown)		
	tianeptine	237.5mg		
	clobazam	18 tablets, dose unknown		
1002908	Keppra	25 to 50g	coma, psychosis, aggression, convulsions.	recovered
	carbamazepine	3g		
	barbexaclon	10 tablets, dose unknown		
2000146	Keppra	27g	agitation, aggression	recovered
	phenytoin sodium	17.5g		
	erythromycin	unknown		
1005220	Keppra	16g	coma, convulsions	recovered
	carbamazepine	25g		
	topiramate	4.2g		
2000031	Keppra	15g	somnolence	recovered
	olanzapine	unknown		
1005499	Keppra	12g	asymptomatic	recovered
1004240	Keppra	5 to 15g	nausea, drowsiness	recovered
2000077	Keppra	unknown	convulsions	recovered

While only one of the cases of overdose (20000549) of Keppra alone was associated with respiratory depression and suppression of consciousness this case was well documented in a preprint of a case study by Barrueto et. al. from

the NYU School of Medicine.¹ This patient had a prescription for only Keppra. A serum screen for other anticonvulsants and a urine screen for drugs were negative. The patient required intubation but recovered without sequela. Five of the six cases where multiple medications were implicated were associated with some degree of suppression of the level of consciousness. Except for one case where follow up was not provided all cases recovered.

Only one case describes impairment in consciousness and respiratory compromise that is not complicated by the presence of the overdose of other medications. This case is so well documented that, along with the supportive cases where other medications are implicated, the requested labeling change should be permitted.

4.2 Patient Package Insert

4.2.1 Sections added because of Reported Medication Errors

As noted above, a number of additions were made to address the problem of medication errors. These included: a warning to the patients to check their medication, _____, and a description of the various formulations. This reviewer agrees these changes.

A number of stylistic changes have been made that include the following: capitalization of KEPPRA throughout, the addition of the registered trademark on page 1, _____ changed to paragraph. These changes appear appropriate.

The following change was made:

KEPPRA has not been approved for children below the age of 16.

The sponsor notes that _____
This seems to be an appropriate change.

The following changes have been made regarding the administration of tablets:

Take KEPPRA with or without food. Swallow the tablets whole. Do not chew or crush _____

The Sponsor notes that this change has been carried out to _____
_____ This section was previously removed by this division's revision. This reviewer would expect that another, perhaps more important reason, for this may be the effect crushing or chewing would have on absorption and bioavailability. Thus, the new wording may promote this sort of

¹ This article has been accepted by the journal of Toxicology-Clinical Toxicology.

administration in patients who feel they can tolerate the taste. Perhaps it is better to leave as presently written.

The following bulleted items have been added under the question of "How should I take Kepra?"

- "Tell your healthcare provider if your seizures get worse or if you have
- "Talk to your healthcare provider about what to do if you miss a dose."

These are similar to the following statements that the Division previously edited out:

- "Tell your doctor if your seizures get worse or if you have any new types of seizures."

The first statement was added to the PPI, according to the Sponsor, to promote communication with the practitioner. The Sponsor notes that changes in the seizure characteristics may change the practitioner's choice in treatment and dosing. This is true. The issue is whether this sort of patient education belongs in the PPI. This reviewer feels the statement may be left in.

The second statement was added to ' One reason that the original statement was removed is that the instructions were too specific. Different providers may have different ways of dealing with missed medications. The present statement is less specific and appears appropriate to this reviewer. The question may be asked if this sort of patient education belongs in the PPI. This reviewer, however, agrees with the statement.

Changes similar as those made in the PI regarding dye were made to the PPI. The appropriateness of these changes is dependent on chemistry's review.

5. CMC Issues

In the approvable letter the Sponsor was reminded of prior agreements:

Moreover they were also reminded that while the Division has not completed validation of the regulatory methods we expected the Sponsor's continued cooperation to resolve any problems that may be identified.

The Sponsor agreed to all issues raised. Dr. Broadbent, chemistry reviewer is presently reviewing this issue.

6. Promotional Material

The Sponsor included promotional material. No problems were observed with the information provided in these materials.

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N. Hershkowitz MD,PhD
Medical Reviewer

J. Feeney, M.D. _____

3 Draft Labeling Page(s) Withheld

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Norman Hershkowitz
7/10/03 04:49:13 PM
MEDICAL OFFICER

John, Note, I have also attached the reveiewto theold
label change CBE that I discuussed in the
review

John Feeney
7/10/03 05:36:55 PM
MEDICAL OFFICER

I concur with Dr.Hershkowitz's assessments and believe the current
submission supports an Approval action. The division should
continue to monitor name confusion with Kaletra. The
anti-viral division has been notified of the potential
for confusion.

Clinical NDA Review

Brand Name:	Keppra
Generic Name:	Levetiracetam
Sponsor:	UCB Pharma, Inc.
Indication:	Seizures of Partial Onset
NDA Number:	21-505
Original Receipt Date:	June 20, 2002
Clinical Reviewer:	Norman Hershkowitz MD, PhD
Review Completed:	April 16, 2003

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1 Background

Keppra (levetiracetam) was approved by the FDA for the adjunctive treatment in partial onset epilepsy on 30 November 1999 (NDA 21-035). It is available in 3 doses in tablet form (120, 500 and 750 mg). The recommended dosage is 1,000, 2,000 and 3,000 mg administered daily (divided into two doses). The present application consists of a request for approval of a new dosing form, Keppra Oral Solution (10%- 100mg/ml), that is presented as an alternative for adult patients with difficulty swallowing. As such included in this application are the requisite bioequivalence and chemistry data that are being reviewed by Chemistry and Clinical Pharmacology. Also included in this submission is new data on the mechanisms of action of this agent that is under review by Pharmacology. No new clinical efficacy data is included in this application. Information that is under review by the present reviewer includes a safety update. The original submission included safety information on a total of 3,339 patients (data cut-off 30 November 1998). Changes in labeling as well as a new Patient Package Insert are also included and reviewed by this medical officer.

2 Summary and Description of Clinical Data

The most recent complete analysis of safety was the that of safety update included in the evaluation for approval on November 30, 1999. It reported on a total of 3362 unique subjects. A Table presenting a breakdown of information on these patients is presented in the Sponsors Table below.

Table 3-44 Overview of Sources of 3339 Unique Subjects (a) with Safety Data who were Exposed to Levetiracetam and Included in Safety Update to NDA 21-035 (Data Cut-Off Date 30 November 1998 (b))

Groupings of Data Sources and Status at Prior Data cut-off Date		
Clinical Pharmacology Studies	364 subjects	All studies completed
Adult Epilepsy Studies	Total exposure: 1388 ^a patients (including 563 patients in N129 and 280 patients in N147)	Studies ongoing: N129, N147
Paediatric Epilepsy Studies	29 patients (including extension treatment in 2 patients in ^c and 22 in ^d)	
Studies in Other Indications	1558 patients	All studies completed

^a An additional 23 Naïve^b Patients were also exposed to levetiracetam

^b Cut-off date for serious adverse events was 28 February 1999

^c Summary table of adverse events in patients receiving "long-term" levetiracetam was based on 674 patients treated for at least 1 year

Since that time the clinical development of Keppra has continued.

A summary of patients, both newly exposed and those in continuing long term studies, that are examined in the present submission can be found Table 3:2. It should be noted that a majority of reports involving newly exposed patients were not available in a completed format or the studies were ongoing or just recently completed at the time of data cut-off (December 1, 2001¹).

In summary the present submission includes new data derived from the following sources:

1. Three new clinical pharmacology trials have been performed.
2. Nine studies in partial onset seizures have been initiated (6 in adults and 3 in children). Two adults and one pediatric trial are controlled. One controlled trial was for monotherapy but was closed because of poor enrollment.

¹ There was an update for serious adverse events and adverse events resulting in discontinuation of March 1, 2002.

In addition to the new studies the Sponsor includes a careful analysis of updated open label partial onset seizure extension studies that were analyzed at the time of the last safety update (N129 and N147; 617 patients). These studies were subsequently closed. Because the median treatment of exposure of these patients are now longer (2 ½ years) and ranges up to 10 years, UCB has decided to update the analysis by only examining patients with equal or greater than a 6 month exposure. UCB has included additional 1036 patients (included in item #2 above). In the discussions below this is referred to as the study that examines patients with 6 month or greater drug exposure time. This study constitutes a very large part of the data included on safety in patients with seizures of partial origin.

A number of post-marketing efforts were included in this submission. UCB surveyed 774 German patients with partial onset seizures for adverse events who received Keppra for over a 9-month period. An additional 780 patients were provided uninterrupted access to Keppra by a number of mechanisms, the majority of which involved compassionate use. The latter involved the non-systematic collection of adverse event report data from European patients. Lastly, the Sponsor carried out a review of spontaneous post marketing reports. It is estimated that a total of _____ United States and _____ European patients have been exposed to Keppra.

A review of literature revealed only 7 cases of new reported adverse events.

A review of all patients who participated in the present and prior safety update is included in the table (Table 3:2) below.

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Table 3:2 Overview of Levetiracetam Safety Data Included in ISS
 (Data Cut-off Date 01 December 2001^(a))

Patients Previously Included in ISS Safety Update (NDA 21-035)		
Partial Onset Epilepsy	Total exposure \geq 6 months: 1036 patients	Pooled Safety based on: 775 patients in N129 and N147 4 patients in phase 2 studies 66 patients in double blind phase 3 studies 191 patients in other extension studies
	785 patients (included in tally above)	Individual full study reports for: 505 patients in N129 ^(b) and 280 patients in N147
Newly Exposed Patients (Enrolled in Completed Studies with Full or Abbreviated Study Reports)		
Clinical Pharmacology	56 subjects	Single dose studies N01072, N160, and N01002
Partial Onset Epilepsy	40 patients	Studies N158 and N01006 (administratively closed for poor enrollment); 10 patients entered from N147
Newly Exposed Patients (Enrolled in Ongoing or Recently Completed Studies with Interim Reports/Synopses)		
Add-on: Partial Onset Epilepsy	99 adult patients	Recently completed open-label N161
	130 adult patients (blinded)	Ongoing N165 (and its open-label extension N01020) and ongoing N01005
	135 pediatric patients (blinded)	Ongoing double-blind, placebo-controlled N159
	135 pediatric patients	Open-label extension N157 (all patients entered from N129 or N151, previously reported studies)
/	22 patients	Ongoing open-label — and its extension, — and open-label extension —, 16 patients to-date enrolled from N129)
	3 patients (blinded)	Ongoing double-blind, placebo-controlled N166 and —
Other Indications	58 patients	Completed double-blind, placebo-controlled — and ongoing open-label — and its extension —
	64 patients (blinded)	Ongoing double-blind, placebo-controlled —
Ongoing or Recently Completed Phase 4 Studies (with Interim Reports)		
Add-on: Partial Onset Epilepsy	1524 patients	Completed N01030 in U.S. and ongoing N01031 in Europe and Argentina

^(a) Cut-off date for serious adverse events and premature terminations due to adverse events is 01 March 2002

^(b) Ten additional patients received levetiracetam for <6 months and therefore are not included in the pooled safety database; they accrued no additional data after the previous Safety Update data cut-off.

A brief description of all clinical trials performed is included in the table below (Table 3:3). As can be observed many trials are ongoing and therefore complete data is unavailable. Some trials were discontinued because of difficulties with recruitment.

Because vast majority of data presented in this submission consists of open label uncontrolled exposures, safety implications are limited. The original double blind exposures must therefore be considered more definitive.

Table 3:3 Overview of Clinical Studies^(a)

No.	Principal Investigator	Country	Dates of Conduct ^(b)	Clinical Status	Location of Report (Vol. / Page No.)
SINGLE DOSE CLINICAL PHARMACOLOGY STUDIES IN HEALTHY VOLUNTEERS					
N160	DeBruyn	Belgium	3/99 – 4/99	Completed	Section 6 Vol. 25 pg. 1700
N01002	Knops	Belgium	10/99	Completed	Section 6 Vol. 21 pg. 216
N01072	Shenouda	U.S.	8/01	Completed	Section 6 Vol. 22 pg. 563
PARTIAL ONSET SEIZURES					
Controlled Clinical Trials					
N159	Multiple (45)	U.S. / Canada	9/99 – (1/03)	Ongoing	Section 8 Vol. 29 pg. 189
N158	Multiple (38)	U.S.	10/99 – 8/00	Discontinued	Section 8 Vol. 30 pg. 628
N01006	Multiple (37)	U.S.	4/00 – 1/01	Discontinued	Section 8 Vol. 30 pg. 628
N01005	Multiple (9)	Taiwan	11/00 – (2/02)	Ongoing	Section 8 Vol. 30 pg. 534
N165	Multiple (58)	Japan	1/01 – (1/03)	Ongoing	Section 8 Vol. 30 pg. 370
Uncontrolled Clinical Trials					
N129 ^(c)	Multiple (93)	Europe	12/93 – 9/01	Completed	Section 8 Vol. 40 pg. 3838
N147 ^(c)	Multiple (43)	U.S.	5/96 – 7/00	Completed	Section 8 Vol. 84 pg. 19645
N157 ^(c)	Multiple (29)	U.S. / Canada	2/98 – (2005)	Ongoing	Section 8 Vol. 111 pg. 29356
N161	Multiple (6)	Australia	7/00 – 9/01	Completed	Section 8 Vol. 39 pg. 3750
N01010	Multiple (6)	U.S.	(--) – (11/02)	Ongoing	Section 8 Vol. 24 pg. 1538
N01020 ^(c)	Multiple (3)	Japan	11/02 – (--)	Ongoing	Section 8 Vol. 112 pg. 29488
Controlled Clinical Trials					
/	Multiple (30)	U.S./Canada/Europe	/	Ongoing	Section 8 Vol. 112 pg. 29591
/	Multiple (38)	U.S./Canada/Europe	/	Ongoing	Section 8 Vol. 113 pg. 29696
Uncontrolled Clinical Trials					
/	Multiple (3)	Europe	/	Completed	Section 8 Vol. 113 pg. 29816
/	Multiple (3)	Europe	/	Ongoing	Section 8 Vol. 113 pg. 29969
/	Multiple (3)	U.S./Canada/Europe	/	Ongoing	Section 8 Vol. 114 pg. 30105
Controlled Clinical Trial					
/	Multiple (10)	U.S.	/	Completed	Section 8 Vol. 114 pg. 30165
Uncontrolled Clinical Trials					
/	Multiple (6)	U.S.	/	Ongoing	Section 8 Vol. 114 pg. 30270
/	Multiple (6)	U.S.	/	Ongoing	Section 8 Vol. 114 pg. 30374
Controlled Clinical Trials					
-	Multiple (14)	U.S.	-	Ongoing	Section 8 Vol. 115 pg. 30463
POST-MARKETING STUDIES IN PARTIAL ONSET SEIZURES					
N01030	Multiple (638)	U.S.	3/00 – 7/01	Completed	Section 8 Vol. 115 pg. 30555
N01031	Multiple (140)	Europe/Argentina	8/00 – (1Q03)	Ongoing	Section 8 Vol. 115 pg. 30829

^(a) Data cut-off date for synopses is 01 December 2001.

^(b) First patient enrolled to last patient completed (or projection, if ongoing).

^(c) Extension study with no *de novo* patient enrollment.

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3 Integrated Summary of Safety

3.1 Deaths

At the time of the original submission of this NDA, on November 30, 1998, 31 deaths were noted. Overall mortality rate was 11.5/1,000 patient-years and SUDEP rate was 3.5/1,000 patient-years. The Sponsor updated mortality data in adjunctive partial seizure onset by combining updated analysis of patients for patients exposed for greater than 6 months (1036 patients from N129 and N147) with the recently completed open label study (N161) for a total of 30713 patient-years. The total mortality rate with this updated analysis is now 8.1/1000 patient-years and SUDEP rate is 2.9/1000 patient-years. These values are reduced from previous reported data and are within that expected in this population. It should be noted that this analysis overlaps with the previous analysis; i.e. deaths that were included from studies 129 and 147 that were exposed for greater than 6 months are also included in the present analysis. Thus only 7 out of the 25 patients reported are new to this division. Appendix A gives a listing of all deaths in this analysis as well as narratives on the 7 new patients. There was one SUDEP case in these new reported deaths. There were no particularly suspicious deaths among these cases. A discussion of specific issue of notable new deaths is presented below. It should be noted that interpretation of causality of deaths and other adverse events in this section and others are complicated by the fact that nearly all patients are on multiple anticonvulsants.

One ~~patient~~ patient died while participating in Study ~~1846~~

This patient is included in the 7 new deaths noted above. The narrative of this patient is included in Appendix A. The patient appeared to be suffering from fever and a respiratory infection for 3 days when she had an episode of status and went into cardiopulmonary arrest. This was followed by multiple organ failure and death. The trigger event in this case may have been upper respiratory infection. Considering that this may be an unexpected adverse event this will also be discussed more specifically in a section below.

Patient ISS/ISE 1846 was a 70-year-old with a history of CAD and aortic valve disease who died of an Intracerebral Hemorrhage.

One patient died of cardiac arrest. The death occurred 62 days after starting Keppra. The patients did have some risk factors for CAD including Type II DM and hypertension. In the previous NDA the Sponsor reported no effect of Keppra on apparent effect on PR, QRS or QTc intervals.

Two of the 1524 patients examined in phase 4 studies died. One patient was a 56-year-old with a history of alcoholism and positive HIV treated with Combivir (that has a boxed warning for hepatotoxicity) who was also on phenytoin. Two months after starting Keppra he was admitted for hepatic encephalopathy following a drinking binge. The death certificate noted cirrhosis of the liver and severe alcoholism with hepatic encephalopathy as the cause of death. There does not appear to be an autopsy. There appears to be sufficient although not completely documented information that would indicate that this was not Keppra

related. Hepatic function will however be discussed in a section below. The CRF gave no further information. The second patient is a 36-year-old with a significant history of depression with previous suicide attempts. This patient died of a self-inflicted gunshot wound 79 days after starting Keppra. Suicide is already noted in the Warning section under neuropsychiatric effects of Keppra in the labeling.

Twenty-six post marketing reported death were noted. Ten were described as SUDEP and an additional 9 deaths were related to seizures (status, aspiration etc). Seven patients died from non-seizure related cases. Two patients died of cancer (hepatic and brain). One patient died of bone marrow suppression. The latter patient is known to the division and will be discussed in a separate section on blood dyscrasias below. We have been monitoring for additional such cases. Two patients died from successful suicide attempts. As noted above suicide is already listed under neuropsychiatric adverse events in the warning section of the labeling. A 72 year old man died of a myocardial infarction. Lastly a mother gave birth to a child with a hypoplastic left heart syndrome after taking Keppra during the first 4 weeks of gestation. The child died within one year after birth. The mother was also on fluoxetine that, like Keppra, is labeled as pregnancy category C. There is insufficient information on birth defects presently to make a definitive statement on human teratogenesis. The Sponsor is participating in the National AED Registry. Information on the Registry is included in the labeling.

No deaths were noted in published reports.

Generally, according to this reviewer, there are no unexpected deaths that would require a change in the present labeling.

3.2 Serious Adverse events

3.2.1 Definition and Approach to Serious Adverse Events

Adverse events are presented in terms of COSTART body systems and are grouped into more specific disease system by UCB AE Grouping and Preferred Term.

The Sponsor defined serious adverse events as events that resulted in:

- Death
- Inpatient hospitalization as defined by the institution or including at least one overnight stay at either a hospital, a medical unit, or a permanent institution or an emergency unit of a chronic-care hospital for whatever reason (including for diagnostic procedures)
- Permanent or significant disability/incapacity
- Prolongation of an existing stay in hospital
- Any life-threatening condition (immediate risk of dying)
- Congenital abnormality/birth defect
- Diagnosis of cancer in subject or offspring
- Overdose.

3.2.2 Treatment Emergent Serious Adverse Event

In the ≥ 6 month analysis 365 patients out of 1036 experienced treatment-emergency serious adverse events (TESAE). One hundred and eleven of these events were newly reported since the last safety update. The table below (Table 7:20) presents reported serious adverse events that were observed in 1 % or more of the patients examined in the analysis during the full time period of this study. This includes patients previously reported. Also included in this table are new cases since the prior safety update. As is apparent, as has been previously reported the most common serious adverse events were associated with the CNS; i.e. either seizures or psychiatric. Moreover, the ratio of general classes of adverse events that were reported for the whole study verses those newly reported are similar indicating that at least for such general categories extension of the trial has not found any new remarkable patterns of toxicity.

Table 7:20 Most Common Serious Adverse Events by COSTART Body System
(Reported by 1.0% or More of the Patients Treated for ≥ 6 Months)
(N = 1036)

COSTART Body System / Preferred Term	All Events N (%)	Subset Occurring Since Safety Update Data Cut-off ^(a)
Total No. Patients	363 (35.0%)	111
Body as a Whole	141 (13.6%)	45
Accidental injury	72 (6.9%)	19
Cardiovascular System	31 (3.0%)	12
Digestive System	37 (3.6%)	12
Musculoskeletal System	10 (1.0%)	6
Nervous System	171 (16.5%)	96
Confusion	10 (1.0%)	3
Convulsion	102 (9.8%)	53
Grand mal convulsion	15 (1.4%)	3
Status epilepticus NOS	16 (1.5%)	5
Procedure	85 (8.2%)	16
Procedure diagnostic epilepsy	38 (3.7%)	4
Procedure therapeutic epilepsy	23 (2.2%)	5
Procedure therapeutic NOS	32 (3.1%)	6
Respiratory System	29 (2.8%)	8
Pneumonia	13 (1.3%)	3
Urogenital System	36 (3.5%)	17
Unintended pregnancy	10 (1.0%)	5

^(a) Includes only events reported after the 30 November 1998 data cut-off for the Safety Update

Source: Table 16.4:16 (Section 16); by-patient listing in Listing 18.4:4 (Section 18) Narratives are in Section 20.5

In addition to above serious adverse effects in less than 1% of patients include:

1. Out of a total of 10 unintended pregnancies (5 of which are new) there were 2 congenital anomalies, 2 cases of abortion, 1 case of abnormal labor, ectopic pregnancy, abnormal fetal cardiac rhythm and one case of fibroids. All cases involved patients who were being treated with concomitant anticonvulsants.
2. There are additional 5 new neoplasms reported since the last safety update that included a total of 25 neoplasms. Of the new reported neoplasms 3 were CNS (one was a reoccurrence) and 2 were GI.
3. Deaths are noted in the section above.
4. Previous safety update noted 4 patients with hemic and lymphatic system events (including leukopenia, anemia and thrombocytopenia). These will be discussed in further detail in a later section.
5. There was one case of renal failure. The case of renal failure occurred in a 59 year old male and was also reported as a serious event. Creatinine was found to be 8.4. Upon hospitalization a nephrology consult obtained and believed this may result from drug toxicity. Along with Keppra the patient was on non-steroid anti-inflammatory drugs (salsalate, aspirin, and ibuprofen at different times). Patients were on other anticonvulsants (Tegretol and Neurontin). The patient refused diagnostic procedure and recovered without the need for dialysis. It is unclear if NISAIDS were also discontinued. Reading the CRF this

event appeared following an episode of pneumonia. The issue of renal function will be discussed in subsequent section.

6. There were two cases of "elevated liver function tests or other hepatic abnormalities" reported in the earlier safety report. There are no new cases. Liver function will be discussed in a separate section.

As noted above, nearly all cases reported were observed in patients on multiple anticonvulsants.

In the 40 patients from these studies there was one serious adverse event in the form of CNS lymphoma diagnosed 163 days after starting Keppra.

Of unblinded ongoing trials of 120 patients exposed to Keppra, 3 serious adverse events were reported. They include fracture of radius, pneumonia (recovered with continued treatment). The third is not discussed by the Sponsor.

There were 6 serious adverse events reported in still blinded studies. Three were from accidental injuries; two of these were associated with seizures. Four patients had seizures that were considered serious. One case of seizure required unblinding; it was determined that the patient was receiving Keppra.

The Sponsor performed a separate analysis for _____ patients exposed to Keppra. Thus off 135 in an open label _____ study _____, 20 serious adverse events were reported in 17 patients. Also presented were serious adverse events for study _____ that is a controlled and still blinded protocol. These are summarized in the table below (Table 7:22). In the open label trial _____, convulsions fever and gastroenteritis were the most common events. Most worrisome in this list was the case of "heart arrest." This case has actually been presented in Appendix A as a death. It is a rather complicated case involving pneumonia, status epilepticus and cardio-pulmonary arrest. It is difficult to attribute causality because of the complexity but the triggering event may have been the development of pneumonia. Keppra produces a mild average drop in WBC count, but up to the present time this drop has not been associated with infection. Indeed none of the significant decreases in white blood cells observed in the present submission was associated with a significant infection. The labeling presently includes information from controlled trials that patients exposed to Keppra had a higher incidence on infection than those exposed to placebo.

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Table 7:22 Serious Adverse Events by COSTART Body System in ██████ Patient with Partial Onset Seizures: Ongoing Placebo-controlled, Double-blind Study ██████ and Its Extension Study ██████

COSTART Body System / Preferred Term	Open-Label Study ██████ (N = 135)	Double-Blind Study N159 (N = 135)
No. Patients with SAE	17 (12.6%)	9 (6.7%)
Body as a Whole		
Accidental injury	0	1 (0.7%)
Asthenia	1 (0.7%)	0
Back pain	1 (0.7%)	0
Bacterial infection	1 (0.7%)	0
Fever	2 (1.5%)	0
Unevaluable reaction ^(a)	1 (0.7%)	0
Viral Infection	0	1 (0.7%)
Cardiovascular Disorders		
Cerebrovascular disorder ^(b)	1 (0.7%)	0
Heart arrest	1 (0.7%)	0
Digestive System		
Gastroenteritis	2 (1.5%)	1 (0.7%)
Gastrointestinal disorder ^(c)	1 (0.7%)	0
Hematemesis	1 (0.7%)	0
Ileitis ^(c)	1 (0.7%)	0
Intestinal obstruction	0	1 (0.7%)
Vomiting	1 (0.7%)	0
Metabolic and Nutritional Disorders		
Dehydration	0	2 (1.5%)
Diabetes mellitus	1 (0.7%)	0
Nervous System		
Anxiety	0	1 (0.7%)
Convulsion	3 (2.2%)	1 (0.7%)
Hallucinations	0	1 (0.7%)
Hostility	1 (0.7%)	0
Personality disorder	1 (0.7%)	0
Psychosis	1 (0.7%)	0
Schizophrenic reaction	1 (0.7%)	0
Status epilepticus NOS	2 (1.5%)	2 (1.5%)
Respiratory System		
Pneumonia	0	2 (1.5%)
Urogenital System		
Kidney calculus	1 (0.7%)	0
Hydronephrosis	1 (0.7%)	0
Pyelonephritis	1 (0.7%)	0

^(a) Verbatim term, multi-organ system failure
^(b) Verbatim term, increased intracranial pressure
^(c) Verbatim term, enterovesicular fistula with Crohn's disease
 Source: NDA Section 8; Narratives are in Section 20.5

A total of 325 patients have been enrolled in ongoing trials of ██████. Two patients on placebo had serious adverse event (suicide attempt and back sprain).

Of the 40 patients studied in the double blind ██████ protocol, one on drug had a serious adverse event. She was a 33 year old female with a history of bipolar disorder who attempted suicide.

An open label study on ██████ is ongoing. Four of 18 enrolled patients were noted to have serious adverse events in the form of worsening of the disease under study.

Two patents out of 64 suffered in a study that examined ██████. Both had significant risk factors along with ██████. Both had serious adverse events in the form of CAD related events. Both had significant risk factors along

with diabetes (one including previous history of angina, CHF and hypercholestelema the other with hypertension and hypercholestelema). Patients were 63 and 67 year old. In neither case was drug stopped. The adverse event in one case consisted of hospitalization for a coronary artery stent. In the other case the patient had transient ST depression. The latter patient died of cardiac arrest 42 days after he completed the study.

The German phase 4 study that examined adjunctive treatment in 774 patients over a period of 12 weeks revealed 14 serious adverse events in eight patients. These are listed in the table (7:27) below:

Table 7:27 Serious Adverse Events Reported in German Post-Marketing Survey
(N = 774)

Case No.	Age (years)	Sex	Dose (mg/day)	Total Duration at Onset (days)	Serious Adverse Event(s)
1004396	56	F	2000	15	Vertigo, disturbance in attention (Dose reduced)
			1500	30	Palpitations (Described as irregular heart beat)
1004171	39	F	1000	15	Convulsions NOS aggravated, mental disorder NOS, depression, catatonia (Discontinued)
1004131	43	M	2000	39	Convulsions NOS (Discontinued)
100417	8	F	375	73	Pneumonia NOS (Discontinued)
1003854	77	F	2000	Unknown	Death NOS (Due to underlying disease, cardiovascular and demential disorders)
1003770	19	F	2000	Approx. 1 mo.	Astrocytoma (Pre-existing), brain edema
1003699	37	F	3000	Unknown	Astrocytoma (Pre-existing)
1002957	51	M	1000	14	Grand mal convulsion (Dose increased)

Source: MedWatch forms are provided in Section 20.2

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A summary of common post-marketing serious adverse events may be gleaned from the following table that presents adverse events reported 10 or more patients. The number of which were serious is indicated in the far right column.

Table 7:28 Spontaneously Reported Adverse Events with ≥ 10 Reports *via* Worldwide Post-Marketing Surveillance of Keppra®

MedDRA/System Organ Class/Preferred Term	All Adverse Events	Serious Adverse Events
Gastrointestinal Disorders		
Diarrhoea NOS	13	2
Nausea	13	2
General Disorders and Administration Site Conditions		
Drug interaction NOS	19	7
Fatigue	27	2
Investigations		
Drug level NOS increased	13	1
Weight decreased	15	1
Metabolism and Nutrition Disorders		
Anorexia	16	1
Nervous System Disorders		
Convulsions NOS	20	12
Convulsions aggravated NOS	11	5
Dizziness	20	2
Headache	28	5
Memory impairment	14	2
Somnolence	40	4
Status epilepticus	10	10
Psychiatric Disorders		
Abnormal behavior NOS	12	3
Aggression	39	14
Anger	17	0
Anxiety NEC	14	2
Confusion	12	3
Depression	34	4

MedDRA/System Organ Class/Preferred Term	All Adverse Events	Serious Adverse Events
Hallucination, visual	10	4
Hostility	10	1
Psychiatric Disorders (continued)		
Insomnia	21	2
Irritability	21	1
Mood swings	12	2
Psychotic disorder NOS	12	6
Skin and Subcutaneous Tissue Disorders		
Hypotrichosis	15	0
Rash NOS	16	1

These common post-marketing reports are not completely unexpected from what has already been demonstrated for Keppra and is presently in the label in its label. Keppra induced skin reactions are, however, noted in the labeling to be as common as placebo and will require some additional discussion in a separate section below. Adverse events in up to 9 patients that involves the blood lymphatic system have been reported: leukopenia, thrombocytopenia, drug interactions, suicide ideation and suicide attempt. These will be discussed in a separate section below.

Generally the serious adverse event data is not unexpected. Many of these cases will be discussed in more detail in the following section on adverse events requiring reductions or discontinuation of Keppra.

3.3 Adverse Events Resulting in Dose Reduction or Discontinuations

A dose reduction or discontinuation rate in the controlled trials in the original NDA was 15% for drug treatment group and 11.6 % for placebo group. The most common reason for discontinuation or reductions for the Keppra group were CNS toxicity (behavioral, asthenia, dizziness and somnolence) or seizures. These were the most common reasons for discontinuations and dose reductions seen in the Studies used for the original NDA approval.

The following (Table 7:15) presents a comparison of dose discontinuation or reduction for the complete ≥ 6 month data set and also the subset of new patients (n=45) since prior safety update for most common ($\geq 1\%$) adverse events. The most common reasons for discontinuations or reductions in the data sets were similar to previous studies (i.e. CNS adverse events and seizures). Of the subset of 45 new patients with dose reductions/discontinuations, 18 patients discontinued treatment. A listing of these patients can be found in Appendix B. The most common cause of discontinuation was a result of behavioral adverse events, one of which included attempted suicide. As noted these events are already noted in the Warning section of the labeling. This reviewer's examination of these events identified a number of cases that required closer examination. Thus there was one case of neutropenia observed. The narrative in this case was very brief stating that WBCs were already low when the patient entered (patient was on other anticonvulsants that may lower the white count). Nonetheless examination of the CRF revealed a drop of WBCs from at least 5.5 to 3.2 with the percentage of neutrophils going from 47% to 32%. There was one rash noted. Examination of the CRFs (a narrative could not be found) revealed this consisted of a vesiculobullous rash on the neck that was described as possibly erysipelas. No other information if provided. Presumably this is of infectious origin. As there is a limited discussion of rashes in the labeling and a number of suspect cases these events will be discussed more thoroughly in a separate section below.

Table 7:15 Most Common Adverse Events by COSTART Body System Leading to Discontinuation or Dose Reduction (Reported by 1.0% or More of the Patients Treated for ≥ 6 Months) (N = 1036)

COSTART Body System / Preferred Term	All Events N (%)	Subset Occurring Since Safety Update Data Cut-off ^(a)
Total No. Patients	295 (28.5%)	45
Body as a Whole	92 (8.9%)	
Asthenia	36 (3.5%)	4
Nervous System	197 (19.0%)	
Ataxia	14 (1.4%)	1
Convulsion	65 (6.3%)	10
Depression	13 (1.3%)	3
Dizziness	28 (2.7%)	3
Hostility	10 (1.0%)	2
Nervousness	14 (1.4%)	1
Somnolence	45 (4.3%)	2
Procedure	15 (1.4%)	
Procedure diagnostic epilepsy	12 (1.2%)	1

(a) data cut-off after 30 November 1998.

Source: Table 16.4.12 (Section 16); by-patient listing is in Listing 18.4.3 (Section 18); Narratives are in Section 20.5

Two patients discontinued [redacted] studies ([redacted]) of the total of 40 patients exposed to Keppra 2 discontinued because of adverse events. One case was because of depression one month into treatment. There were situational events that may have contributed to depression. The second case consists of an episode of headache and nausea that was thought to be secondary to an "inner ear dysfunction." The symptoms resolved after drug termination.

In the completed open label trial (N161) on adjunctive treatment in partial epilepsy two patients were reported to have discontinued treatment because of adverse events. One patient was withdrawn because of phenytoin with aggression and somnolence toxicity. A review of the case reveals phenytoin was elevated at the time of entering the study. Moreover, examination of serum levels interactions has failed to identify any such interaction in past pharmacokinetic studies. Another patient was withdrawn because of an episode of post-ictal psychosis.

Off ongoing trial for seizures of partial origin that yet remain blinded (N165 and N101005) 7 patients out of a total of 160 have discontinued. Three discontinued for somnolence and 2 for rash. Another patient discontinued because of a mild thrombocytopenia that resolved on discontinuation. Another was a patient who was taking Keppra who was discovered to have seizure exacerbation that was categorized as serious. This led to unblinding.

The only [redacted] data present, according to the Sponsor, prior to the safety cut-off includes information on the ongoing double blind controlled [redacted] and its open label extension [redacted]. A total of 135 patients are enrolled in [redacted] that still remains blinded. Six patients have discontinued in this study for asthenia, hostility, headache, maculopapular rash, a surgical epilepsy procedure (electrode grid placement) and the last for fever, status epilepticus and multi-organ failure that lead to cardiopulmonary arrest and death. This latter patient is noted in the sections on adverse events and death. The narrative for the patient is in Appendix A. Seven patients of 135 enrolled in [redacted] discontinued treatment. The most common cause of discontinuations was because of behavioral events including aggression, hostility, hyperactivity hallucinations and mood swings. As previously noted behavioral adverse events are starting to appear rather common in the [redacted]. One case of