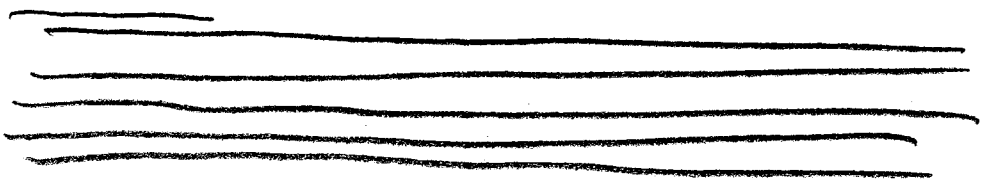
ataxia associated with speech disturbance was noted. Examination of the narrative for the latter revealed this patient to have a rather significant neurologic history including mental retardation, hydrocephalus with a V/P shunt and foot deformity. The patient ataxia and speech impairment (not described) resolved days after Keppra discontinuation. It is noted tat the patient was left with problems of "falling" and with concentration after the event. There is no explanation for these persistent problems. It is premature to attribute this to Keppra as the patient appeared to suffer significant underlying neurologic disease.

3.4 Published Studies

Off the seven published reports identified 4 described psychiatric and 3 described dermatological reactions. These are not classified as serious but will be discussed in this section. The 4 psychiatric reactions occurred in 3 adolescents and 1 child. All of these subjects had some history of cognitive or behavioral dysfunction (e.g. mild mental retardation, depression, "cognitive impairment," learning disability, oppositional behavior). The authors of the article felt that the young age and predisposing cognitive/behavioral history may be predisposing causes for such a response). It should be noted that such behavioral phenomena are already contained in the warning section of the labeling. It however appears rather common in the pediatric population and will have to be more carefully examined when data is complete at the time of the pediatric submission. The reactions included auditory and visual hallucinations, delusions and agitation. Behavioral symptoms resolved when medication was discontinued. The skin reactions are discussed in German manuscript by Bauer et. al. For which an English translation is provided. The skin reactions were described as a "spotted exanthema," and "pruritis with small generalized spotted exanthema." In no case was there a description of anything that may have been described as Stevens Johnson or TEN like reactions. Reactions resolved with steroid treatment and drug discontinuation (2 cases) or a simple dose decrease (1 case). Off note while a rash is noted in the present labeling it is done so in the context that it is more common in placebo treatment groups. Skin reactions will be discussed in separate section below.

3.5 Time of Onset for Adverse Events (long term exposure)

The Sponsor performed a variety of analysis to examine the temporal pattern of adverse event onset in the $\geq$ 6 months pooled database to support the following new labeling claim in Adverse Reaction section:



The table below (Table7:10) presents the common adverse events that were reported for different intervals of exposure. The Sponsor interpreted such data as indicating that while some adverse event classes may or may not be observed more frequently at the earlier stages of exposure all classes of events were observed throughout the study; i.e. there where no class of adverse events seen after 6 months that were not seen earlier in the study. While such conclusions might be made when major body system COSTART changes are grouped, the Sponsor does not critically evaluate more specific types of adverse reactions. For example, there was one case potentially toxic renal failure that occurred after 4 years of continued exposure of drug. There were no such cases reported earlier in this database. There was also one case of cerebral hemorrhage seen over 4 years in the database following treatment for which there were no similar cases seen earlier. Certainly at present it is difficult to attribute such events to the medication but it would be misleading to assume that they were not medication related. The present recommended labeling would assume this to be the case.

Table 7:10 Most Common Adverse Events by COSTART Body System (Reported by 10% or More of the Patients Treated for ≥ 6 Months) Categorized by Period of Onset (N = 1036)

COSTART Body System / Preferred Term	≥ 1 day-≤ 6 mo. (N=1036)	≥ 6 mo.- ≤ 1 yrs. (N=1035)	>1 -≤ 2 yrs. (N=830)	>2 -≤ 3 yrs (N=581)	>3 -≤ 4 yrs. (N=440)	>4 -≤ 5 yrs. (N=351)	>5 yrs. (N=171)
Body as a Whole	629 (60.7%)	430 (41.5%)	433 (52.2%)	270 (46.5%)	198 (45.0%)	142 (40.5%)	69 (40.4%)
Abdominal pain	61 (5.9%)	30 (2.9%)	39 (4.7%)	27 (4.6%)	11 (2.5%)	9 (2.6%)	3 (1.8%)
Accidental injury	146 (14.1%)	123 (11.9%)	143 (17.2%)	83 (14.3%)	68 (15.5%)	61 (17.4%)	26 (15.2%)
Asthenia	202 (19.5%)	55 (5.3%)	54 (6.5%)	17 (2.9%)	16 (3.6%)	14 (4.0%)	6 (3.5%)
Back pain	53 (5.1%)	16 (1.5%)	47 (5.7%)	18 (3.1%)	21 (4.8%)	13 (3.7%)	6 (3.5%)
Flu syndrome	65 (6.3%)	51 (4.9%)	56 (6.7%)	37 (6.4%)	17 (3.9%)	15 (4.3%)	3 (1.8%)
Headache	193 (18.6%)	106 (10.2%)	103 (12.4%)	58 (10.0%)	34 (7.7%)	23 (6.6%)	14 (8.2%)
Infection	183 (17.7%)	129 (12.5%)	120 (14.5%)	72 (12.4%)	68 (15.5%)	35 (10.0%)	21 (12.3%)
Pain	91 (8.8%)	50 (4.8%)	62 (7.5%)	47 (8.1%)	44 (10.0%)	23 (6.6%)	10 (5.8%)
Cardiovascular System	67 (6.5%)	36 (3.5%)	90 (10.8%)	52 (9.0%)	21 (4.8%)	27 (7.7%)	22 (12.9%)
Digestive System	277 (26.7%)	134 (12.9%)	192 (23.1%)	109 (18.8%)	71 (16.1%)	63 (17.9%)	44 (25.7%)
Diarrhea	61 (5.9%)	34 (3.3%)	33 (4.0%)	27 (4.6%)	13 (3.0%)	12 (3.4%)	10 (5.8%)
Nausea	62 (6.0%)	17 (1.6%)	39 (4.7%)	15 (2.6%)	7 (1.6%)	3 (0.9%)	4 (2.3%)
Hemic and Lymphatic System	60 (5.8%)	38 (3.7%)	51 (6.1%)	40 (6.9%)	23 (5.2%)	19 (5.4%)	9 (5.3%)

Table 7:10 Most Common Adverse Events by COSTART Body System (Reported by 10% or More of the Patients Treated for ≥ 6 Months) Categorized by Period of Onset (N = 1036) (Continued)

COSTART Body System / Preferred Term	≥ 1 day-≤ 6 mo. (N=1036)	≥ 6 mo.- ≤ 1 yrs. (N=1035)	>1 -≤ 2 yrs. (N=830)	>2 -≤ 3 yrs (N=581)	>3 -≤ 4 yrs. (N=440)	>4 -≤ 5 yrs. (N=351)	>5 yrs. (N=171)
Nervous System	558 (53.9%)	351 (33.9%)	358 (43.1%)	229 (39.4%)	136 (30.9%)	111 (31.6%)	46 (26.9%)
Convulsion	105 (10.1%)	100 (9.7%)	113 (13.6%)	60 (10.3%)	29 (6.6%)	30 (8.5%)	13 (7.6%)
Depression	61 (5.9%)	39 (3.8%)	39 (4.7%)	25 (4.3%)	15 (3.4%)	7 (2.0%)	6 (3.5%)
Dizziness	134 (12.9%)	46 (4.4%)	51 (6.1%)	30 (5.2%)	32 (7.3%)	14 (4.0%)	1 (0.6%)
Insomnia	36 (3.5%)	22 (2.1%)	32 (3.9%)	23 (4.0%)	13 (3.0%)	9 (2.6%)	3 (1.8%)
Nervousness	67 (6.5%)	16 (1.5%)	21 (2.5%)	7 (1.2%)	11 (2.5%)	4 (1.1%)	1 (0.6%)
Somnolence	178 (17.2%)	41 (4.0%)	36 (4.3%)	15 (2.6%)	13 (3.0%)	8 (2.3%)	4 (2.3%)
Tremor	44 (4.2%)	16 (1.5%)	34 (4.1%)	13 (2.2%)	14 (3.2%)	5 (1.4%)	1 (0.6%)
Respiratory System	194 (18.7%)	132 (12.8%)	159 (19.2%)	102 (17.6%)	67 (15.2%)	55 (15.7%)	28 (16.4%)
Pharyngitis	75 (7.2%)	42 (4.1%)	50 (6.0%)	25 (4.3%)	23 (5.2%)	10 (2.8%)	8 (4.7%)
Rhinitis	64 (6.2%)	36 (3.5%)	34 (4.1%)	36 (6.2%)	23 (5.2%)	12 (3.4%)	8 (4.7%)
Skin and Appendages	135 (13.0%)	67 (6.5%)	93 (11.2%)	64 (11.0%)	42 (9.5%)	28 (8.0%)	17 (9.9%)
Rash	47 (4.5%)	24 (2.3%)	39 (4.7%)	24 (4.1%)	16 (3.6%)	7 (2.0%)	3 (1.8%)
Special Senses	132 (12.7%)	68 (6.6%)	75 (9.0%)	41 (7.1%)	28 (6.4%)	17 (4.8%)	15 (8.8%)
Urogenital System	123 (11.9%)	84 (8.1%)	117 (14.1%)	69 (11.9%)	44 (10.0%)	42 (12.0%)	13 (7.6%)
Urinary tract infection	29 (2.8%)	29 (2.8%)	39 (4.7%)	21 (3.6%)	19 (4.3%)	10 (2.8%)	4 (2.3%)

Source: Table 16.4.9 (Section 16)

A similar analysis is made with laboratory results (see Appendix G). While generally the Sponsors labeling conclusions are justified there was one case of a possibly significant elevation in serum creatinine that was not seen prior to 6 months.

Lastly, there is insufficient information as to how carefully patients who dropped-out for reasons that were presumably other then adverse events were monitored for treatment related adverse events..

3.6 Adverse Events of Interest

3.6.1 Hematological

Abnormalities in WBC and neutrophil count were noted in the original NDA application such that approximately twice the number of patients on Keppra then on placebo experienced significant decreases in WBC and neutrophil counts. No patient discontinued because of these changes and all but one abnormality returned to baseline following discontinuation of Keppra. There is also a very minor but statistically significant reduction in red cell indices when compared to placebo (i.e. a 0.038% drop in hematocrit). Original labeling includes information on treatment related minor reduction various blood indices in the. Because of a total of 20 post-marketing cases of blood abnormalities received after NDA approval, additional information was added to "Adverse Reactions" under "Postmarketing Experience" in te leabeling. Thus, cases of leukopenia, neutropenia, pancytopenia and thrombocytopenia are described.

Previous $\geq$ 6 month analysis identified 70 patients with significantly low WBC and 50 with low neutrophil counts. Since this update 26 new patients were identified having low white cell abnormalities (WBC, neutrophils or lymphocytes) based upon predetermined criteria or reported as an adverse event. A summary of these can be found in the table below (Table 10:7). None of these were associated with clinically significant sequela; i.e. hospitalization or infection.

Table 10:7 Overview of New Cases of WBC Abnormalities (Decreases) Since the Safety Update

ISS/ISE No.	Parameter(s)	PCS[a] (yes/no)	Adverse Event	Outcome
1758	Neutrophils	No	Leukopenia	Still present (therapeutic/diagnostic procedure performed)
1916	WBC	No	Leukopenia	Recovery (no action taken)
1985	Neutrophils	No	Leukopenia	Still present (verbatim, chemotherapy induced)
1994	Neutrophils	Yes	None	–
2116	WBC	Yes	None	–
2346	WBC	No	Leukopenia	Recovery (no action taken)
2405	Neutrophils	Yes	None	–
2417	Lymphocytes	Yes	Pancytopenia	Recovery (no action taken)
2461	Neutrophils	Yes	Leukopenia	Still present (no action taken)
2466	Lymphocytes	Yes	None	–
2521	Lymphocytes	Yes	None	–
2614	Lymphocytes	Yes	None	Flu syndrome reported 4 days prior
2673	Neutrophils	Yes	None	–
2840	WBC	Yes	Leukopenia	Recovery (no action taken)
2858	WBC	Yes	None	–
2922	WBC	Yes	Leukopenia	Recovery (dose decreased/ discontinued)
2970	WBC	No	Leukopenia	Recovery (no action taken)
3024	Neutrophils	Yes	None	–
3050	WBC	Yes	None	–
3066	WBC	Yes	None	–
3198	WBC	Yes	None	–
4951	Neutrophils	Yes	None	–
4952	Neutrophils	No	Leukopenia	Recovery (no action taken)
5004	WBC	No	Leukopenia	Recovery (prescription drug administered)
5096	Neutrophils	Yes	Blood dyscrasia	Sequelae (therapeutic/diagnostic procedure)
5104	WBC	Yes	None	–
	Neutrophils	Yes	None	–

[a] Value met pre-specified criteria for possibly clinically significant low values: $\leq 2.8 \times 10^9$/L for WBC count and ≤15% or $\leq 1.0 \times 10^9$/L for neutrophil count

No patients in newly initiated studies have experienced serious adverse events or discontinued treatment because of white cell abnormalities. No patients in the German Phase 4 study experienced serious adverse events or discontinued Keppra for this same reason.

During the commercial use of Keppra there have been 5 cases of serious adverse events reports of leukopenia and 2 of neutropenia that have been categorized by the Sponsor as of moderate significance. Six cases are from Germany. The duration till the adverse event varied from 5 to 60 days. All patients were taking concomitant medications. Of the leukopenia cases three resolved on the discontinuation of Keppra. One case resolved with Keppra continuation. Little information is available on one case of leukopenia. One case of neutropenia resolved with continuation of Keppra whereas the second case resolved with the discontinuation of Keppra.

The Sponsor also notes 4 reports of more significant WBC abnormalities in post marketing reports. Narratives for these are included in Appendix C. These have been followed by the division. One patient had a previous history of pancytopenia that worsened upon Keppra treatment and subsequently improved when Keppra was discontinued. The second involved a patient with Lupes and a previous history of leukopenia. The patient was on Phenobarbital and Oxcarbazepine. The patient was hospitalized for sepsis secondary to pancytopenia. Bone marrow suggested aplastic syndrome. All AEDs were discontinued and the patient recovered. The third case involves a [redacted] girl with a history of

pancytopenia who Keppra was started to replace Divalproex treatment because of thrombocytopenia. Soon after receiving Keppra the patient developed pancytopenia. Steroids were started and Keppra continued and platelet count improved. The last, and perhaps most worrisome case, is that of a 22 year old man who developed sever pancytopenia with no WBCs. The patient died of an intracerebral hemorrhage. This patient was on multiple anticonvulsant medications. The most recent medication, however, was Keppra. Except for the last case these cases are somewhat equivocal because of a previous history of some form of low cell count. Interestingly two cases are associated with lupus. Two of the cases (the last two noted) are domestic and two are European. The division is presently monitoring for additional cases of aplastic anemia. This reviewer feels that a change in labeling may not be needed at the present time.

In the last ≥ 6month analysis 6 patients were identified has having significant low platelets counts. None of these patients had Keppra decreased for this reason. In the new update 2 additional patients have been noted to have had significantly decreased platelet counts with an additional two additional patients reported as having thrombocytopenia as an adverse event. All patients continued medication. One of these patients was reported to have an accompanying leukopenia and another anemia. In no case was the thrombocytopenia reported as serious.

One patient of all newly initiated studies discontinued treatment because of thrombocytopenia (reduction is just below cut off range). Platelets returned upon discontinuation.
One patient in the German post marketing study was a reported to have a mild thrombocytopenia that was attributed to Depakote. No information is presented as to whether Keppra was continued, but the thrombocytopenia was reversed.

Eight case of thrombocytopenia and 1 case of thrombocytopenia purpura were reported in spontaneous post-marketing reports. For one case there is insufficient information to comment. Fives cases had reversal of thrombocytopenia with continuation of Keppra. The reversal in these cases were frequently associated the discontinuation of either AED other then Keppra (frequently Valproic acid) and/or the initiation of steroids. In one case the thrombocytopenia resulted from an overdose of multiple medications. Although improvement occurred there is no note as to whether Keppra was discontinued. Off these 9 reports Keppra was discontinued in two cases with resolution of thrombcytopenia. As compared to the general mild reduction in platelets in the other cases these two cases involved dramatic drops in platelet s. Platelets were as low as 6000/mm^3 in one such case and occurred in patient who was described to have developed idiopathic thrombocytopenia purpura. The platelets returned to near normal following discontinuation of Keppra and steroid treatment. The last case is perhaps the most worrisome case. This involved 34-year-old women with vasculitis who was on multiple medications. In the other case, platelets declined to a value as low as 3000/mm^3. The patient's platelets dropped to 26,000/mm^3 following treatment with Keppra. Keppra was discontinued by platelets dropped to 3,000/mm^3. Patient received steroids and a platelet infusion. The patient remained hospitalized on Keppra and no further information is contained in the submission. When this reviewer examined updated information from AERs he was able to determine that platelets recovered upon ivIg treatment and Keppra discontinuation; which brings the total number of cases with discontinuation of Keppra to 3. The final diagnosis was thought to be most likely idiopathic thrombocytopenia purpura. Perhaps because of this diagnosis there is mention that the patients neurologist as planing to restart the Keppra.

In the prior safety cutoff there were 26 patients with significant reduction in hemoglobin values in the ≥ 6 month analysis. Since this time an additional 4 patients developed significant reductions. None of these new patients had serious adverse events, dose reductions or discontinuations associated with the low hemoglobin indices.

None of the newly initiated clinical studies in partial epilepsy or other indications has reported serious adverse events or discontinuations because of anemia.

No patients in the German phase 4 reported anemia as a serious adverse event. There were two reported in post marketing. One was reported as anemia and the other as erythropenia.

The data presented above would not indicate any changes to present labeling, however, significant changes should continue to be monitored carefully.

3.6.2 Hepatic Function

It is noted in the present labeling, under Precautions, that no significant changes have been observed in liver function indices during clinical trials. It is however noted that one patient, in open label studies, discontinued treatment because of liver function test elevation.

Controlled trials in the original NDA revealed elevated but comparable proportions of liver function abnormalities (approximately 1.4 %) in control and placebo group. This could be accounted for by the multiple anticonvulsants that the enlisted patients were using. Of the new safety analysis for patients exposed to $\geq$ 6 months, 12 significant increases in LFTs were noted. None of these were noted to be serious. One patient discontinued treatment with Keppra. A narrative could not be found on this patient and the CRF was in German. It can only be said that the adverse event was not reported as serious.

No patients has either discontinued treatment or experienced a serious adverse event of all newly initiated studies (i.e. seizure and other disorders).

One patient from the phase 4 studies (N01030 and N01031) developed hepatic encephalopathy and died. Liver failure was presumably a result of alcoholic induced cirrhosis. This case is noted above in the section on deaths.

There have been 3 reported cases of hepatic toxicity in post marketing reports. One case is rather complicated and because of this it is difficult to attribute causality of any particular agent. It involves a 21 year old female who had a recent history of withdrawal from multiple anticonvulsants because of LFT elevation. She was started on Keppra and one week latter presented in status epilepticus that was difficult to control with benzodiazepines, phenytoin and phenobarbital. Complex I deficiency was diagnosed. Liver biopsy revealed "acute hepatitis." There was no mention of causality. Other problems observed in this hospitalization included adrenal insufficiency, pancreatitis, pneumonia and sepsis. It is noteworthy the Complex I deficiciency has been associated with liver failure. The second case involved a 39 year old man on multiple medications who was admitted for what appeared to be urosepsis with elevated LFTs. Antibiotic were administered and the condition improved with Keppra continuation. There is little information on the last case which involved a 17 year old girl hospitalized with elevated LFTs and positive monospot test 1 ½ months following the initiation of Keppra.

The above information would not require an alteration in labeling. Nonetheless, there needs to be maintained vigilance.

3.6.3 Renal

In the control studies of the original NDA safety review no difference could be found between control or drug treatment groups mean values of creatinine or BUN. In the initial application there was one case each of kidney failure, kidney function abnormal and decrease in creatinine clearance. These patients were continued on medication and enrolled in to the continuation trials for which the 6 month or greater exposure analysis was performed. There was one new patient with renal failure, already noted in the section on serious adverse events. The patient had what appeared to be 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.

From the $\geq$ 6 month study there was only one patient with significantly elevated creatinine ($\geq$ 2 mg/dl) who had been previously identified in the original NDA safety update. There was also 26 patients (8 of whom are new) with significantly elevated BUN ($\geq$60 mg/dl). Treatment was continued and in all but two values returned to normal. No adverse events were reported in these patients.

One patient in one of the phase 4 studies also exhibited renal failure. This 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 topiramte's labeling to indicate an association with glomerulonephritis .

No renal failure was reported in post marketing reports according to the to the sponsor.

There is no discussion in the present label on effects of Keppra induced renal toxicity.

While there is no convincing argument that Keppra is renal toxic there are two cases of pathology that has been attributed to other drugs that the patient was receiving while onceiving Keppra. There is no need for label change at present time but there should be continued vigilance to such a potential effect.

Two [redacted] cases in ongoing studies were identified with kidney stones and reported as a serious adverse event in two ongoing [redacted] trials. The first occurred in an [redacted] with a history of hematuria and urinary crystals. The second case occurred in an [redacted] who presented with symptoms and signs of renal stones that spontaneously resolved. A definitive diagnosis became evident when the patients was latter started on nephrolithogenic agent topiramate. As these studies are ongoing it is unclear if these patients received Keppra or placebo.

Examination of the urinalysis results from ≥ 6 month study appeared to be surprisingly abnormal. 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 percent of abnormal UA values seemed rather high to this reviewer. It should however be noted that these are cumulative results for an extended time period (median exposure of 2 ½ years). Moreover, such data are difficult to analyze because of the lack of placebo comparative data. Very likely the high protein, RBCs and WBCs represent urinary tract infection. Perhaps this is related to the fact that patients on Keppra appeared to have a greater incidence for infection then placebo in the original NDA controlled trials. There is no specific mention of such abnormalities in the present labeling nor is there a discussion in the previous NDA medical review. While nor requiring labeling changes, we might ask the Sponsor for more information on such cases.

3.6.4 Skin Reactions

There was no difference in the original NDA controlled studies between suspected allergic reactions in control and placebo treated patients. Indeed examination of label reveals greater incidence of rash in the placebo then in the drug treated group. Because published reports have described potential skin reactions this class of adverse events will be discussed.

It should first be noted that no new skin reactions were described as "Toxic epidermal necrolysis" or "Stevens-Johnson syndrome." There has been in a total of 7 cases of skin reactions that have required reductions or discontinuations of Keppra in the 6 month or greater extended open label study. Of these 3 are new. One case, previously noted was a case of erysipelas that required a dose discontinuation and therefore more likely represented an infection. Another case was not classically allergic in that it was described as eczematoid and only required a dose reduction. The last case was that of a potential allergic rash that was described as vesiculobullous. It was however only described as mild intensity and Keppra was not discontinued but the dose was reduced.

There were no allergic reactions reported in the newly initiated studies. No adverse events involving potentially allergic skin reactions were reported I the phase 4 studies.

There were 4 cases described in postmarketing reports. In one case it was unclear if there was a de-challenge although the patient recovered. Three cases resolved with Keppra discontinuation but the rash

in one returned without a re-challenge. The cases are described as exfoliative dermatitis, toxicoderma and "red, itchy rash."

Three cases of a skin reaction are reported in a single German publication[2]. These were discussed above. The skin reactions were described as a "spotted exanthema," and "pruritis with small generalized spotted exanthema." In two cases rash resolved days after the discontinuation of Keppra. Keppra was only decreased in the third case with resolution of the rash within days.

This reviewer believes that while rashes do not appear serious there may be sufficient evidence to include skin rash in the section on post-marketing experience.

3.6.5 Conclusions

Adverse events as revealed in this submission do not differ in detail from those previously reported during the original NDA review. The interpretation of the data is however limited by the general lack of a control group. Thus again CNS (seizures and behavioral symptoms) appear to be the most common serious adverse events observed. There are no more cases of blood dyscrasias that would indicate any updated labeling changes since post-marketing information was added. Such, cases, however, need to be monitored for. There were two cases of renal failure that were potentially toxic. While this is not sufficient to draw conclusions regarding Keppra causality and altar labeling there should be increased vigilance for such cases. The Sponsor may be asked for an analysis of the abnormal UA results (the high incidence if WBCs, RBCs and protein). This should not hold up the approval status of the submission as this likely represents a cumulative incidence of urinary tract infections. This reviewer does feel that there may be a sufficient number of new cases of potentially allergic skin reactions to add to the post-marketing section of the labeling.

4 Labeling

The labeling changes are described in a tabular format which is included in the Appendix D. What follows is a discussion of each recommended labeling change organized by section. The reader is asked to refer to Appendix D for a description of the Sponsor recommended changes.

4.1 Description

This describes the new oral solution. The reader is referred to chemistry's review.

4.2 Clinical Pharmacology

4.2.1 Mechanisms of Action

The revised section describes data that differentiates Keppra from classical anticonvulsants and concludes that [redacted] Of note, no information is included on effects on voltage gaited

[2] Epileptlogie 14: 23-24, 2001.

sodium channels although studies exist this channel[3]. According to this published report Keppra has no effect on this channel. Blockade of this channel is thought to be the predominate mechanism of action for phenytoin and carbamazepine. Perhaps more importantly this reviewer wonders whether it may be premature to conclude that its mechanism of action is unique. This is somewhat promotional and to prove the negative (no effect) there needs to be a preponderance of data. The reader, however, is referred to the review by Dr. Fisher, the Pharm/Tox reviewer.

4.2.2 Pharmacokinetics, Overview

This notes that Keppra tablets and oral solution are bioequivalent. This reviewer has no comment regarding this revision but the reader is referred to the review by PK.

4.2.3 Pharmacokinetics, Absorption and Distribution

This describes the bioequivalence of oral solution and tablets in terms of rate and extent of absorption. This reviewer has no comment regarding this revision but the reader is referred to the review by PK.

4.2.4 Pharmacokinetics, Pharmacokinetic Interactions

This section introduces studies performed that examined drug interactions and makes one change to clarify information contraceptives changed to oral contraceptives. It also introduces studies on drug interactions involving valproate and probenecid. This reviewer has no comment regarding this revision but the reader is referred to the review by PK.

4.2.5 Pharmacokinetic, Special Populations, Pediatric Patients

This is a change for clarity that describes pediatric studies what was previously described as [redacted] and is know described as "body weight adjusted apparent clearance." This reviewer has no comment regarding this revision but the reader is referred to the review by PK.

4.3 Clinical Studies

4.3.1 Effectiveness in Partial Onset Seizures

A sentence was added to better describe Study 3 to parallel one that already describes study 1 and 2; i.e. "Patients enrolled in Study 3 (N138) had refractory partial onset seizures for at least 1 year and had taken [redacted] The Sponsor refers to the original NDA application. As this was not available Dr. Friedman's medical review of the original NDA was used to confirm information. This review indicates that patients were selected so that they were refractory on a "*maximal of one anticonvulsant*" (occasional benzodiazepines were allowed for seizure control). It appears to this reviewer

[3] Zona et. al. Seizure, 10(4):267-286, 2001;

that the statements of "[redacted]" should be changed to "1 classical anticonvulsant." Because of this error I called Patty A. Fritz, VP of Regulatory Affairs at UCB, on 4/3/03. She investigated this and agreed that this was an error. She agreed to my revised changes (see Appendix F for a copy of e-mail communication from UCB).

The second labeling change in this section is as follows. The sentence "During the baseline period, patients had to have experienced at least [redacted] partial onset seizures during each 4-week period." is changed to read "During the baseline period, patients had to have experienced at least two partial onset seizures during each 4-week period." This is accurate and appropriate[4].

This reviewer recommends that the following additional sentence be added to this application, [redacted]

4.3.2 Study 1

The Sponsor requests to change the sentence:
The 18-week treatment period consisted of a [redacted] titration period, followed by a [redacted] fixed dose evaluation period, during which concomitant AED regimens were held constant.
To:
The 18-week treatment period consisted of a [redacted] titration period, followed by a [redacted] fixed dose evaluation period, during which concomitant AED regimens were held constant.

Examination of the original review material indicates that the presently approved sentence is correct and this change should not be permitted. Discussions in the 4/3/03 teleconference with Patty Fritz confirm this. She agrees to withdraw the requested change (see Appendix F).

4.4 Contraindications

In this section the Sponsor wishes to change the following section from:

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

To:

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

The addition of oral solution is appropriate and should be allowed.

4.5 Warnings-Neuropsychiatric Adverse Events

The Sponsor has alphabetized a listing of adverse events in 6th paragraph of this section. This is acceptable.

4.6 Precautions

4.6.1 Information for Patients

The following sentence has been added to this section of the labeling:

---

[4] The number of minimum seizures per 4-week periods during the baseline for studies N051, N132 and N138 were 4,2, and1, respectively.

Physicians should advise patients and caregivers to read the patient information leaflet which appears as the last section of the labeling.

This refers to a document entitled "Patient Information [redacted] that is also included in this submission. This can be considered a Patient Package Insert (PPI) and will be discussed below.

This is appropriate. The FDA is presently requesting Sponsors to submit PPIs for all drug submissions.

4.6.2 Drug Interactions

A sentence was changed from:

Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic studies [redacted] and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients.

To:

Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic studies (phenytoin, valproate, oral contraceptive, digoxin, warfarin, and probenecid) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients.

Valproate and probenecide was added so this introduction sentence completely reflects inforamtion that is discussed latter in this section. This appears justified. The Sponsor notes that "contraceptive" was changed to "oral contraceptive" but the examination of the label reveals that it already states "oral contraceptives." PK should comment on the acceptability of studies and the inclusion of this information.

4.6.3 Drug Interactions, Drug-Drug Interaction between Keppra and Other Antiepileptic Drugs

Two new paragraphs describing two PK studies examining the interaction between Keppra with Phenytoin and Valproate were added. The information in these paragraphs are based upon old (N143) as well as new (N160) PK studies. PK should comment on the acceptability of studies and the inclusion of this information.

A minor alteration in this section is a list of AEDs that have now been alphabetized. This is acceptable.

4.7 Precautions- Pregnancy Exposure Registry

The Sponsor is changing the following sentence from:

To facilitate monitoring fetal outcomes of pregnant women exposed to Keppra®, physicians [redacted] before fetal outcome is known (e.g., ultrasound, results of amniocentesis, etc.), in the Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free).

To:

To facilitate monitoring fetal outcomes of pregnant women exposed to Keppra, physicians should encourage patients to register, before fetal outcome is known (e.g., ultrasound, results of amniocentesis, etc.), in the Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free).

The Sponsor notes this change reflects the "requirement for patients to register in the registry." No other information is provided. A scientific rounds given at the FDA on 4/2/03 by the principal investigator of this registry, Dr. L Holmes, confirms this. He noted the normal protocol is that physicians recommends to the patient that she registers. This was confirmed on a call to the tool free number fro the registry. I was informed that when physicians call they are usually requested to have the patients call themselves. This is done for a number of reasons, but most prominent is that of confidentially. It is also generally believed that because the registry involves 3 interviews that patients who take the initiative to call are more likely to follow through.

4.8 Adverse Reactions - Long Term Exposure

The Following section has been added in Adverse Reaction under the sub-heading of

This reviewer feels that the sort of analysis that was carried out to come to this conclusion is insufficient to justify the present statement. The reader is referred to section 3.4 (Tome of Onset for Adverse Events) n the present review.

4.9 Overdosage

The Sponsor wishes to change this section that reads:

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.
To:
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.

This adds a number of additional symptoms observed during overdose. The Sponsor has backed this up with sufficient number of cases to allow this change.

Off note the division has recently received a CBE labeling supplement (SLR 025) for overdosage labeling changes. This adds some additional signs and symptoms in addition to those that are presently being added. These include depressed level of consciousness, coma, and respiratory depression. While not yet formally reviewed this reviewer has told the CSO that it is justified.

4.10 Dosage and Administration

The Sponsor wishes to change the dosing section from:

Treatment should be initiated with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. -

To:

Treatment should be initiated with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg.

While the new statement is accurate this reviewer is concerned that this new information placed in dosing will tend to promote the use of higher doses. Perhaps it would be best to change this section as follows:

Treatment should be initiated with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg.

4.11 How Supplied

This describes the oral solution. Chemistry should comment on this change.

4.12 Manufacturing Information

A new manufacturer is added for the solution that is different from that which produces the tablets. Chemistry should comment.

4.13 Patient information Leaflet

Included in this submission is a "Patient information — This appears to be a Patient Package Insert (PPI). This PPI is presented below with track changes. Where my changes are substantive comments are included in the footnotes. DDMAC and DSRCS has performed a separate review.

2 Draft Labeling Page(s) Withheld

[redacted]

5 Pharmacokinetics Review

Dr. Kumi, reviewer for Clinical Pharmacology, has found the solution bio-equivalent and acceptable. All PK labeling changes are acceptable to Dr. Kumi. Of note, some PK changes in labeling were not commented on by Dr Kumi. Most notable here is the PK study examining phenytoin/Keppra interactions. Dr. Kumi noted these were not included because they were previously submitted and reviewed by OCPB.

[redacted]

The OCPB team leader confirmed that all changes are adequate and all new information not commented by Dr. Kumi has been previously reviewed.

6 Chemistry Review

Dr. Broadbent has completed his final review but finds no major issues, and feels it should be approved. There are minor labeling changes and recommendations that were previously discussed with the Sponsor .

7 Pharmacology Review

Has completed their review. Recommendations are similar to those suggested by this reviewer and solely consist of labeling changes.

Appendix A-Summary of Deaths

Tabulation of all deaths analyzed from trials on partial onset seizures. These include previous reported patients as well as 7-newly-reported deaths.

Table 10:17 Summary of Deaths in Epilepsy Patients Treated with Levetiracetam in UCB-Sponsored Clinical Trials (Total Number Exposed = 1662)

ISS/ISE No.	Age (yrs)	Sex	Race	Dose (mg/day)	Time on Drug (days)	Cause of Death[a]
163	68	Female	Caucasian	500	469	Hepatoma
165	64	Male	Caucasian	500	1	Glioblastoma multiforme
174	65	Male	Caucasian	2000	51	Glioblastoma multiforme
179	84	Male	Caucasian	1500	2335	Aspiration pneumonia (following status epilepticus)
1739	43	Male	Caucasian	3000	258	SUDEP
1846[c]	68	Male	Caucasian	4000	1287	Cerebral hemorrhage
2061	62	Male	Caucasian	4000	--	Pneumonia
2091	22	Male	Caucasian	4000	845	Aspiration pneumonia
2141	47	Male	Unknown	2000	151	SUDEP
2275	45	Male	Caucasian	2500	104	Lung cancer
2284[c]	55	Male	Caucasian	4000	1379	"Quadriparesis. Glioblastoma of the brainstem"
2330	56	Female	Caucasian	3000	85	Left ventricle wall complicating acute myocardial infarct, cardiac tamponade
2392	62	Male	Caucasian	4000	545	SUDEP
2432	25	Female	Black	4000	551	Cardiopulmonary arrest (gastric adenocarcinoma)
2475	59	Male	Caucasian	1000	616	SUDEP
2553	37	Female	Hispanic	3000	204	SUDEP
2641	40	Male	Black	3000	229	SUDEP
2772[c]	28.5	Male	Caucasian	4000	1468	"Sudden death (respiratory and cardiac arrest)"

(Continued)

ISS/ISE No.	Age (yrs)	Sex	Race	Dose (mg/day)	Time on Drug (days)	Cause of Death[a]
2776	46	Male	Caucasian	4000	410	Heart failure due to myocardial infarction
2875	53	Male	Unknown	3000	186	Astrocytic glioblastoma (recurrence)
2940[b]	44	Male	Caucasian	--	--	Suicide
4900[c]	47.6	Male	Caucasian	3000	422	SUDEP
4913[b]	28	Male	Unknown	--	--	SUDEP
4942[c]	70	Male	Caucasian	1000	394	"Cardiac insufficiency"; immediately followed "pneumonia"
—[c,d]	—	Female	Caucasian	5000	286	Multi-system failure, hypoxic ischemic encephalopathy, and seizure disorder
N01059[c,e]	63	Male	Caucasian	--	41 post	Cardiac arrest

[a] Attributed to SUDEP if: 1) the victim suffered from epilepsy; 2) the victim died unexpectedly while in a reasonable state of health; 3) the death occurred "suddenly" (in minutes) when known; 4) the death occurred during normal activitiesand benign circumstances; 5) an obvious medical cause of death was not found; and 6) the death was not the direct result of status epilepticus or of direct trauma due to seizure.
[b] Not on Serious Adverse Events listing (Listing 18.4:5, Section 18 Part 2) because total duration of treatment was less than 6 months.
[c] Patient newly reported in Safety Update.
[d] Subject 157/375.
[e] Subject 010/006.

Narratives on 7 newly reported deaths in clinical trials on partial onset epilepsy:

ISS/ISE No. 1846 was a 70 year old male at the time of death whose last study of Participation was Study N129 (Subject 267/001). At the time of the event, he was receiving levetiracetam 4000 mg/day, valproate, and phenytoin. After approximately 3 years and 8 months on treatment, he became unwell and lost consciousness. He was admitted to the hospital where he died a few hours later. On autopsy, the cause of death was determined to be an intracerebral hemorrhage. The Investigator considered that the relationship between the adverse event and the study drug was unlikely. There was a previous history of stroke and long-term anticoagulant therapy.

ISS/ISE No. 2284 was 57 years old at the time of death. He was participating in Study N129 (Subject 234/001) and had received levetiracetam for approximately 4 years when he was hospitalized for asthenia and quadriparesis, which led to an inability to walk; study drug was discontinued. The levetiracetam dose at the time was 4000 mg/day; he was also receiving valproate and carbamazepine. One month later, a highly malignant glioblastoma of the brain stem was diagnosed and the subject died approximately 3 months after the last dose of levetiracetam. The investigator considered that the relationship between the adverse event and the study drug was unlikely.

ISS/ISE No. 2772, a 30-year old male, died while participating in Study N129 (Subject 348/008). He had been receiving levetiracetam for approximately 4 years and 2 months, most recently at a dose of 4000 mg/day. He was also receiving valproate and carbamazepine. He attended a party in the afternoon and banged his head on falling down during a seizure. He was taken to the hospital and an x-ray showed fracture of the skull. He subsequently developed status epilepticus, which progressed to respiratory arrest, cardiac arrest, and death. The investigator considered that the relationship between the adverse event and the study drug was unlikely.

ISS/ISE No. 4900, a 49-year old male had a sudden unexplained death. He was participating in Study N129 (Subject 187/028). He had been receiving levetiracetam for approximately 15 months, receiving 3000 mg/day at the time of his death. He was also being treated with phenytoin. He fell out of his bed and his wife found him dead. No autopsy was performed. The Investigator considered that there was no relationship between the adverse event and the study drug, the event being considered as a sudden death in epilepsy, with coronary heart disease and hypercholesteremia as contributing factors.

ISS/ISE No. 4942, a 70-year-old male was participating in study N129 at the time of death (Subject 337/0130). He had a history of angina pectoris, hypertension, myocardial infarction, and heart failure. He had been receiving levetiracetam 1000 mg/day for approximately 13 months. Other concomitant medications included valproate and clonazepam. He was hospitalized for surgery because of a stenosis of the right femoral artery. He developed sepsis, his status deteriorated, and he died 6 days later. No autopsy was performed. The Investigator considered that there was no relationship between the adverse event and the study drug.

The patient, a [redacted] old Caucasian girl, had a history of epilepsy since infancy, mental retardation, and behavioral problems. She had undergone a right temporal lobectomy and ventilation tube placement in the ears. She had had a stroke at age 8, mild cerebral palsy since age 10, and attention deficit hyperactivity disorder since age 12. After receiving levetiracetam for at least 9 months (preceded by participation in double-blind, placebo-controlled Study N159 which is still blinded), the patient experienced symptoms of a respiratory infection and fever. The levetiracetam dose was 5000 mg/day. The patient symptoms worsened, culminating 3 days later in status epilepticus. En route to the emergency room, she went into respiratory arrest and subsequently cardiopulmonary arrest. Although the patient was resuscitated, she progressed to multi-system organ failure. Life support was terminated and the cause of death was determined as multi-system failure, hypoxic ischemic encephalopathy, and seizure disorder. An autopsy was not performed. The Investigator judged these events as not related to study drug.

A 63 year old man, Subject 010/006 in Study N01059, died. He had a history of Type II diabetes, hypertension, shoulder and back pain, environmental allergies, and erectile dysfunction. The patient had taken levetiracetam for 62 days and died of cardiac arrest 41 days after the last dose of study drug. The investigator considered that the relationship between the death and the study drug was unlikely. None of these new patients were discontinued from the study.

Appendix B- Summary of Discontinuations

The following table includes new patients who discontinued Keppra in evaluation of Open Label study for patients exposed to duration 6 months or more treatment.

Table 7:16 Overview of Patients Who Discontinued Due to Adverse Events (Since 30 November 1998, Data Cut-off Date for Previous Safety Update)

ISS/ISE No.	Age (yrs)[a]	Sex	Race	Dose (mg/day)	Days[b] on Drug	Verbatim Adverse Event(s)[c] [COSTART Term.] Relationship (Comments)
1853	27	M	Cauc.	4000	1806	Herpes zoster infection with pneumonitis[c] [herpes zoster, pneumonia] Possible
1873	33	F	Cauc.	4000	1795	Suspected erysipelas [vesiculobullous rash] Unlikely
2071	59	M	Cauc.	4000	2334	Increase hysterical behaviour [personality disorder] Probable
2521	58	M	Cauc.	3000	1683	Acute renal failure [kidney failure][c] Unlikely (post-pneumonia; dizziness also included on listing)
2772	28	M	Cauc.	4000	1815	Sudden death (respiratory and cardiac arrest)[c] [death] Unlikely (banged head on falling down during a seizure with resulting skull fracture)
2815	34	M	Cauc.	3000	1493	Increased levels of Gamma GT, increased level of ASAT:ALT [GGT increased, SGPT increased] Possible (confusion also cited in termination comments)
2990	40	M	Cauc.	3000	510	Slight increase of number of seizures (some of them with falls) [convulsion] Possible
3030	47	M	Cauc.	2500	939	Caecum cancer with metastases, right hypogastric pain and abnormal faeces[c] [gastrointestinal carcinoma, abdominal pain, abnormal stools] Unlikely
3046	28	M	Cauc.	3500	775, 928	Mild anxieties, depression [anxiety, depression] Unlikely
4900	47	Male	Cauc.	3000	549	Sudden unexpected death[c] [SUDEP] None

Table 7:16 Overview of Patients Who Discontinued Due to Adverse Events (Since 30.November 1998, Data Cut-off Date for Previous Safety Update) (Continued)

ISS/ISE No.	Age (yrs)[a]	Sex	Race	Dose (mg/day)	Days[b] on Drug	Verbatim Adverse Event(s)[c] [COSTART Term.] Relationship (Comments)
4923	43	M	Cauc.	1000	354	Paranoid symptoms [paranoid reaction] Probable
4935	26	M	Cauc.	1000	275	Neutropenia [leukopenia] Possible (following a series of dose reductions over a period of 8 months from 2500 mg/day)
4942	70	M	Cauc.	4000	492	Cardiac insufficiency[c] [heart failure] None (fatal outcome)
5025	24	F	Cauc.	3500	231	Depression, suicide attempt/drug overdose[c] [depression, intentional overdose] Possible (non-fatal, patient ingested a "handful" of lamotrigine, gabapentin, levetiracetam, mesalamine, and other unspecified drugs; the only reported clinical signs were slurring of speech and nystagmus)
5035	23	M	Cauc.	1500	317	Aggression [hostility] Possible
5037	34	M	Cauc.	4000	882	Dizzy and lightheaded [dizziness] Unlikely (occurred following an earlier dose reduction due to confusion; other events included in the termination comments are more aggressive headache and confusion)
5043	21	F	Cauc.	4000	745, 775	Anorexia, sickness [anorexia, malaise] Unlikely, Possible
5099	36	M	Cauc.	4000	191	Combative behavior [hostility] Possible

[a] As reported on Listing 18.4:3; age on case narrative may differ since the narrative reports age at time of event
[b] At onset of adverse event(s)
[c] Also reported as a serious adverse event

Appendix C-Narratives for WBC post Marketing Reports

Narratives for serous WBC count abnormalities from post-marketing reports.

Case 1003527, a 24-year old Belgian man with a history of myoclonus due to a progressively degenerative disease, hypothyroidism, intermittent thrombocytopenia, neutropenia, and pancytopenia underwent a bone marrow biopsy. The biopsy showed thrombocyte dysplasia. At that time valproate was discontinued. Ten months later, he experienced pancytopenia and hepatic cytolysis attributed to Alpharix® (influenza polyvalent vaccine). Five months later, the pancytopenia was still present. The patient was previously treated with piracetam and started treatment with levetiracetam 2000 mg/day 1 year and 7 months after the initial bone marrow biopsy. Concomitant medications included lamotrigine and clonazepam. After approximately 2 weeks, the patient™s platelet count was 80/mm 3 ; RBC, WBC, absolute neutrophil count, eosinophils, basophils, and monocytes were also low. He required a transfusion for pancytopenia. His lowest reported platelet count, 27,000/mm 3 , 40 days after the start of Levetiracetam. Levetiracetam was discontinued and the platelet counts began to improve. One month later, the patient™s pancytopenia was reported to improve.

Case 10036352, a 37-year old German woman with a history of systemic lupus and epilepsy was started on levetiracetam 2000 mg/day in November 2000. She has had leukopenia in the past (as low as 2500/µL). Concomitant medications included phenobarbital, oxcarbazepine, and propolis (a non-prescription medication). The dose of levetiracetam was titrated to 4000 mg/day but was decreased to 2000 mg/day a few days prior to her hospitalization because of irritability. The patient was hospitalized 7 months after starting levetiracetam for sepsis attributed to pancytopenia (leukocytes 2000/µL). Bone marrow biopsy showed an aplastic syndrome and toxic agranulocytopoiesis. There were also signs of autoimmune hemolysis in the context of the known systemic lupus. All AEDs were discontinued, and the patient was treated with steroids and filgastrim. The pancytopenia resolved over 1 month.

Case 2000131, a [redacted] woman in the United States with a history of complex partial seizures, hypothyroidism, and low neutrophil counts developed pancytopenia prior to the first dose of levetiracetam. At that time she was receiving divalproex and thyroid replacement therapy. Her platelet count range was 11,000/mm 3 to 19,000/ mm 3 , and she was asymptomatic. Levetiracetam was started at 67mg/kg/day to replace divalproex which was coincidentally withdrawn. The patient received corticosteroids for her low platelet counts and showed improvement in all blood hematologic parameters. Soon after starting levetiracetam, the patient became pancytopenic again, and received a platelet transfusion. Her platelet count improved (269,000/mm 3 about 1 month later) and she is continuing on levetiracetam therapy.

Case 2000114, a 22-year old man in the United States was hospitalized 3 months after starting levetiracetam 1000 mg/day appearing pale and not feeling well. Concomitant medications included gabapentin (approximately 6 months), carbamazepine (approximately 4 years), depakote (approximately 18 months), and topiramate (approximately 4 years). Laboratory on admission revealed a hemoglobin of 6 mg/dL, platelets 12 (units not provided), and no WBCs. The patient™s mother reported his iebone marrow had been destroyedIt. All medications were discontinued with the exception of depakote. The patient had a brain bleed and died 4 days later.

Appendix D-Outline for Sponsors Labeling Changes

The following provides labeling changes provided by the Sponsor. Note the changes from the presently approved labeling is denoted by bolded entries.

Table 1:1 Summary of Proposed Changes—Package Insert (Changes from NDA 21-035 labeling, approved 22 May 2002 (SLR 013 and 019)

Section	Proposed Changes	Explanation for Change
DESCRIPTION	Description of oral solution added Inactive ingredients for oral solution added	Section updated to reflect new dosage form
CLINICAL PHARMACOLOGY, Mechanism of Action	Section changed: "The antiepileptic activity of levetiracetam was assessed in a number of animal models of epileptic seizures. Levetiracetam did not inhibit single seizures induced by maximal stimulation with electrical current or different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization. Levetiracetam also displayed inhibitory properties in the kindling model in rats, another model of human complex partial seizures, both during kindling development and in the fully kindled state. The predictive value of these animal models for specific types of human epilepsy is uncertain. **Second paragraph deleted.** *In vitro* and *in vivo* recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity. **Levetiracetam at concentrations up to 10 µM did not demonstrate binding affinity [redacted] such as benzodiazepine, GABA (gamma-aminobutyric acid), glycine, NMDA (N-**	Section updated to reflect new mechanism of action information available.

Table 1.1 Summary of Proposed Changes—Package Insert (Changes from NDA 21-035 labeling, approved 22 May 2002 (SLR 013 and 019)

Section	Proposed Changes	Explanation for Change
	methyl-D-aspartate) re-uptake sites or second messenger systems. [redacted]	
CLINICAL PHARMACOLOGY, Pharmacokinetics, Overview	Sentence added: "Levetiracetam tablets and oral solution are bioequivalent."	Section updated to reflect bioequivalence data for tablets vs. oral solution.
CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption and Distribution	Sentence changed to "The oral bioavailability of levetiracetam tablets is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption."	Section updated to reflect bioequivalence data for tablets vs. oral solution.
CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetic Interactions	Second paragraph changed to "Potential pharmacokinetic interactions of or with levetiracetam were assessed in clinical pharmacokinetic studies (phenytoin, valproate, warfarin, digoxin, oral contraceptive, probenecid) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients (see PRECAUTIONS, Drug Interactions)."	Sentence changed for clarity. Sentence updated to add reference to valproate and probenecid interactions. Contraceptives changed to contraceptive.
CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Pediatric Patients	Sentence changed to "The body weight adjusted apparent clearance of levetiracetam was approximately 60% higher than in adults."	Sentence updated for clarity.
CLINICAL STUDIES, Effectiveness in Partial Onset Seizures	Sentence added: "Patients enrolled in Study 3 had refractory partial onset seizures for at least 1 year and had taken 1 or more classical AEDs." Last sentence changed to: During the baseline period, patients had to have experienced at least two partial onset seizures during each 4-week period	Sentence added to describe design of study 3; number of partial onset seizures during baseline corrected to more accurately describe study design.

Table 1:1 Summary of Proposed Changes—Package Insert (Changes from NDA 21-035 labeling, approved 22 May 2002 (SLR 013 and 019)

Section	Proposed Changes	Explanation for Change
CLINICAL STUDIES, Study 1	Sentence corrected: "The 18-week treatment period consisted of a [redacted] titration period, followed by a [redacted] fixed dose evaluation period, during which concomitant AED regimens were held constant."	Correction to study design information
CONTRAINDICATIONS	Sentence changed to: "This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in Keppra tablets **or oral solution.**"	Section updated to reflect new dosage form
WARNINGS, Neuropsychiatric Adverse Events	Listing of behavioral symptoms in sixth paragraph alphabetized	Updated for clarity
PRECAUTIONS, Information for Patients	Sentence added [redacted]	Section updated to reflect addition of new patient information
PRECAUTIONS, Drug Interactions	Third paragraph changed: "Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic studies (phenytoin, **valproate, oral contraceptive, digoxin, warfarin, probenecid**) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients."	Sentence changed for clarity and to add reference to valproate interaction study.

Table 1:1 Summary of Proposed Changes—Package Insert (Changes from NDA 21-035 labeling, approved 22 May 2002 (SLR 013 and 019)

Section	Proposed Changes	Explanation for Change
PRECAUTIONS, Drug Interactions, Drug-Drug Interactions Between Keppra And Other Antiepileptic Drugs (AEDs)	New paragraphs added: **"Phenytoin** **Keppra (3000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy. Pharmacokinetics of levetiracetam were also not affected by phenytoin.** **Valproate** **Keppra (1500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers. Valproate 500 mg twice-daily did not modify the rate or extent of levetiracetam absorption or its plasma clearance or urinary excretion. There also was no effect on exposure to and the excretion of the primary metabolite, ucb L057."** First sentence of third paragraph changed: "Potential drug interactions between Keppra and other AEDs (**carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone and valproate**) were also assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies."	Sections added to described phenytoin and valproate interaction studies.
PRECAUTIONS, Pregnancy Exposure Registry	Paragraph changed: "To facilitate monitoring fetal outcomes of pregnant women exposed to Keppra, **physicians should encourage patients to register**, before fetal outcome is known (e.g., ultrasound, results of amniocentesis, etc.), in the Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free)."	Sentence updated to reflect requirement for patients to register in the registry.

Table 1:1 Summary of Proposed Changes—Package Insert (Changes from NDA 21-035 labeling, approved 22 May 2002 (SLR 013 and 019)

Section	Proposed Changes	Explanation for Changes
ADVERSE REACTIONS	[redacted]	[redacted]
OVERDOSAGE, Signs, Symptoms And Laboratory Findings Of Acute Overdosage In Humans	Additional sentence added: [redacted]	New sentence added to reflect overdose information available.
DOSAGE AND ADMINISTRATION	Third paragraph changed: "Treatment should be initiated with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. [redacted]	Section updated to reflect available long term exposure data.
HOW SUPPLIED	Information concerning Oral Solution added: "**Keppra® (levetiracetam) oral solution 100 mg/mL is a clear, grape-flavored liquid. It is supplied in 16 fl oz amber glass bottles (NDC 50474-001-60) and 16 fl oz white HDPE bottles (NDC 50474-001-48).**"	Section updated to reflect new dosage form.
Manufacturing information	Manufacturing information updated: "**Tablets manufactured by UCB S.A. B-1420 Braine l'Alleud (Belgium)** **Oral Solution manufactured by Mallinckrodt Inc. Hobart, NY 13788**"	Section updated to reflect new dosage form.

Appendix E- Narratives for Post-marketing Skin Reactions

Narratives for post-marketing skin reactions:

Case 1004203, a 38-year old woman started levetiracetam 1000 mg/day. She had a history of toxicoderma while taking carbamazepine, lamotrigine, and oxcarbazepine. Sixteen days later, she developed toxicoderma. Levetiracetam was discontinued and she recovered within 3 days.

Case 1004568, a 27-year old woman started levetiracetam 1000 mg/day and was titrated to 3000 mg/day. Concomitant medications included lamotrigine, valproate, and omeprazole. She had also received cefixime for an unknown indication. Approximately 3 months after starting levetiracetam she developed a generalized polymorphic eruption suggestive of toxicoderma, which was confirmed by skin biopsy. Levetiracetam was discontinued with initial improvement in the skin lesions. One month later, new skin lesions appeared and a second skin biopsy was again consistent with toxicoderma.

Case 1003058, a 56-year old woman developed exfoliative dermatitis 6 days after starting levetiracetam therapy. Concomitant medications included clonazepam and oxcarbazepine. She recovered without sequelae.

Case 2000094, a 51-year old woman was started on levetiracetam 1000 mg/day. Concomitant medications included lamotrigine, felbamate, risperidone, and pergolide. After 25 days, she experienced a red, itchy rash requiring hospitalization. Levetiracetam was discontinued and treatment with prednisone initiated. A dermatologist was consulted and felt the patient™s condition represented a non-specific dermatitis with excoriations.

Appendix F-UCB e-mail Regarding Errors to Labeling Changes

The following is a copy of an -mail sent by Patty Fritz, VP of Regulatory affairs UCB, on 4/3/03 in response to our teleconference of that day.

Dear Dr. Hershkowitz,

To follow up on our conservation this morning:

* The change requested in our NDA in the labeling, specifically the Section entitled, "CLINICAL STUDIES (Effectiveness in Partial Onset Seizures)" reads "Patients enrolled in Study 3 had refractory partial onset seizures for at least 1 year and had taken 1 [redacted] classical AEDs". It should be revised as follows "Patients enrolled in Study 3 had refractory partial onset seizures for at least 1 year and had taken 1 classical AED".
* The last sentence of the same section mentioned above refers to Study 3 (N138). Study 1 (N132) did have a similar inclusion criteria however patients had to have a minimum of 12 partial onset seizures per 12 weeks with a minimum of 2 partial onset seizures per 4 weeks.
* The change requested in the labeling section entitled, CLINICAL STUDIES (Effectiveness In Partial Onset Seizures) Study 1, read "The 18-week treatment period consisted of a [redacted] titration period, followed by a [redacted] fixed dose evaluation period, during which concomitant AED regimens were held constant." This should be changed back to the text that is in the currently approved labeling for Keppra. This should read, "The 18-week treatment period consisted of a 6-week titration period, followed by a 12-week fixed dose evaluation period, during which concomitant AED regimens were held constant." This accurately reflects the design as written in the protocol and the report of the study. The primary endpoint was analyzed including both the titration and the evaluation periods.

Attached is revised labeling redlined with the changes for your convenience (all of the above mentioned revisions are on Page 5 of the attached labeling). Please feel free to contact me should you have any questions. Have a nice day!

kind regards,
Patty Fritz
770-970-8585

Appendix G. Significant Laboratory Abnormalities for ≥ 6 month pooled database

The following tables present defined significant laboratory abnormalities that occurred within distinctive time epochs for the pooled ≥ month database.

Table 8:3 WBC and Differential Counts that Meet Criteria for Possibly Clinically Significant Abnormalities (Adults with Partial Onset Epilepsy on Levetiracetam for 6 Months or Greater): Number (%) Patients with Onset within Time Interval

Parameter		Interval of Onset						
		1 d. - ≤6 mo.	>6 mos. - ≤1 yr.	>1 yr. - ≤2 yrs.	>2 yrs. - ≤3 yrs.	>3 yrs. - ≤4 yrs.	>4 yrs. - ≤5 yrs.	> 5 yrs.
WBC	N	1034	1019	820	570	433	346	168
	Low	44 (4.3%)	21 (2.0%)	21 (2.5%)	11 (1.9%)	8 (1.8%)	9 (2.6%)	4 (2.4%)
	High	2 (0.2%)	2 (0.2%)	2 (0.2%)	2 (0.3%)	0	1 (0.3%)	0
Neutrophils	N	1033	1018	819	570	433	346	168
	Low	33 (3.2%)	14 (1.4%)	16 (1.9%)	11 (1.9%)	7 (1.6%)	3 (0.9%)	4 (2.4%)
Lymphocytes	N	1033	1018	819	570	433	346	168
	Low	6 (0.6%)	2 (0.2%)	5 (0.6%)	2 (0.3%)	3 (0.7%)	3 (0.9%)	0
	High	9 (0.9%)	7 (0.7%)	10 (1.2%)	6 (1.0%)	3 (0.7%)	3 (0.9%)	0
Monocytes	N	1033	1018	819	570	433	346	168
	High	4 (0.4%)	4 (0.4%)	1 (0.1%)	1 (0.2%)	2 (0.5%)	1 (0.3%)	0
Basophils	N	1032	1018	819	570	433	346	168
	High	10 (1.0%)	4 (0.4%)	2 (0.2%)	0	0	0	0
Eosinophils	N	1033	1018	819	570	433	346	168
	High	28 (2.7%)	18 (1.7%)	18 (2.2%)	13 (2.2%)	5 (1.1%)	9 (2.6%)	5 (3.0%)

Source: Table 16.5:4 (Section 16)

Table 8:28 Electrolyte Abnormalities That Meet Criteria for Possibly Clinically Significant Abnormalities (Adults with Partial Onset Epilepsy on Levetiracetam for 6 Months or Greater): Number (%) Patients with Onset within Time Interval

Parameter		Interval of Onset						
		1 d. - ≤6 mo.	>6 mos. - ≤1 yr.	>1 yr. - ≤2 yrs.	>2 yrs. - ≤3 yrs.	>3 yrs. - ≤4 yrs.	>4 yrs. - ≤5 yrs.	> 5 yrs.
Potassium	N	1030	1009	820	570	430	344	168
	Low	6 (0.6%)	1 (0.1%)	1 (0.1%)	0	0	0	0
	High	88 (8.5%)	56 (5.4%)	69 (8.3%)	70 (12.1%)	48 (11.0%)	35 (10.0%)	22 (13.0%)

Source: Table 16.5:4 (Section 16).

Table 8:20 Renal Function Test Results That Meet Criteria for Possibly Clinically Significant Abnormalities (Adults with Partial Onset Epilepsy on Levetiracetam for 6 Months or Greater): Number (%) Patients with Onset within Time Interval

Parameter		Interval of Onset						
		1 d. - ≤6 mo.	>6 mos. - ≤1 yr.	>1 yr. - ≤2 yrs.	>2 yrs. - ≤3 yrs.	>3 yrs. - ≤4 yrs.	>4 yrs. - ≤5 yrs.	> 5 yrs.
Creatinine	N	1034	1020	820	571	432	345	169
	High	0	0	0	0	1 (0.2%)	0	0
Urea	N	1034	1019	819	571	431	345	169
	High	9 (0.9%)	5 (0.5%)	4 (0.5%)	6 (1.0%)	9 (2.1%)	4 (1.1%)	4 (2.4%)

Source: Table 16.5:4 (Section 16)

Table 8:24 Glucose Measurements That Meet Criteria for Possibly Clinically Significant Abnormalities (Adults with Partial Onset Epilepsy on Levetiracetam for 6 Months or Greater): Number (%) Patients with Onset within Time Interval

Parameter		Interval of Onset						
		1 d. - ≤6 mo.	>6 mos. - ≤1 yr.	>1 yr. - ≤2 yrs.	>2 yrs. - ≤3 yrs.	>3 yrs. - ≤4 yrs.	>4 yrs. - ≤5 yrs.	> 5 yrs.
Glucose	N	1027	1015	819	571	433	346	168
	Low	23 (2.2%)	12 (1.2%)	8 (1.0%)	8 (1.4%)	6 (1.4%)	5 (1.4%)	3 (1.8%)
	High	7 (0.7%)	8 (0.8%)	5 (0.6%)	7 (1.2%)	4 (0.9%)	2 (0.6%)	3 (1.8%)

Source: Table 16.5:4 (Section 16)

Table 8:16 Liver Function Test Abnormalities That Meet Criteria for Possibly Clinically Significant Abnormalities (Adults with Partial Onset Epilepsy on Levetiracetam for 6 Months or Greater): Number (%) Patients with Onset within Time Interval

Parameter		Interval of Onset						
		1 d. - ≤6 mo.	>6 mos. - ≤1 yr.	>1 yr. - ≤2 yrs.	>2 yrs. - ≤3 yrs.	>3 yrs. - ≤4 yrs.	>4 yrs. - ≤5 yrs.	> 5 yrs.
N AST	High	1029 2 (0.2%)	1016 4 (0.4%)	816 5 (0.6%)	569 1 (0.2%)	432 1 (0.2%)	345 1	169
N ALT	High	1034 11 (1.1%)	1020 10 (1.0%)	819 5 (0.6%)	571 5 (0.9%)	432 1 (0.2%)	345	169
N GGT	High	1034 68 (6.6%)	1020 53 (5.1%)	819 66 (8.0%)	571 39 (6.7%)	432 25 (5.7%)	345	169
N T. Bilirubin	High	1034 3 (0.3%)	1019 1 (0.1%)	818 1 (0.1%)	571 1 (0.2%)	431 0	345	169
N Alk. Phos.	High	1034 1 (0.1%)	1020 1 (0.1%)	819 2 (0.2%)	571 0	432 2 (0.5%)	345	169

Source: Table 16.5:4 (Section 16)

Table 8:34 Mean (S.D.) Laboratory Parameter Values for Patients on Levetiracetam for 6 Months or Greater: Other Laboratory Tests (Adults with Partial Onset Epilepsy)

Parameter (units)	Baseline	Time on Levetiracetam							
		1 d. - ≤ 6 mo.	6 mo. - ≤ 1 yr.	1 yr. - ≤ 2 yrs.	2 yrs. - ≤ 3yrs.	3 yrs. - ≤ 4 yrs.	4 yrs. -≤ 5 yrs.	≥5 yrs.	Final On-Treatment
N	1029	1029	1016	815	568	431	344	169	1029
Total Protein (mg/dL)	7.2 (0.50)	7.2 (0.72)	7.3 (0.60)	7.3 (0.66)	7.3 (0.65)	7.3 (0.65)	7.4 (0.64)	7.2 (0.67)	7.3 (0.48)
N	997	997	645	410	26	13	2	-	997
Albumin (mg/dL)	4.6 (0.40)	4.7 (0.51)	4.7 (0.50)	4.7 (0.52)	5.0 (0.50)	5.1 (0.48)	4.2 (0.21)	-	4.6 (0.40)
N	1015	1015	1001	804	560	426	339	165	1015
Calcium (mg/dL)	9.3 (0.46)	9.2 (0.65)	9.3 (0.56)	9.3 (0.64)	9.3 (0.71)	9.4 (0.70)	9.4 (0.63)	9.5 (0.69)	9.3 (0.46)
N	6	6	1	-	-	-	-	-	6
Phosphorus (mg/dL)	3.4 (0.64)	3.3 (0.64)	3.7 (-)	-	-	-	-	-	3.6 (0.23)
N	1025	1025	1013	813	566	428	341	167	1025
Uric Acid (mg/dL)	4.2 (1.44)	4.0 (1.73)	4.1 (1.61)	4.0 (1.70)	4.1 (1.70)	4.0 (1.70)	4.1 (1.73)	3.8 (1.73)	4.1 (1.46)

Source: Table 16.5:1 (Section 16) for complete tabulation, including change from baseline and descriptive summaries for subsets of patients by duration on levetiracetam; Table 16.5:2 (Section 16) for summary of baseline and final on-treatment results, with statistical testing.