The **pharmacological activity and safety pharmacology** of levetiracetam was evaluated in mice, rats, hamsters, and guinea pigs. Levetiracetam demonstrated protection in a number of animal models of chronic epilepsy involving genetic and kindled animals with spontaneous, recurrent seizures. It was not active in the classical models of maximal electroshock and pentylenetetrazol seizures in mice. Seizure suppression with levetiracetam was obtained with a moderate safety margin between the doses inducing seizure protection and CNS adverse effects. Levetiracetam exhibited potential antiepileptogenic activity by its ability to inhibit the development of kindling in both mice and rats. Seizure suppression derives from the parent compound. The major metabolite, ucb L057, displayed no significant seizure protection. The R-enantiomer, ucb L060 has only a very weak potency. Anxiolytic effects in the absence of sedation, and improved cognitive function were observed in stressed animals. The therapeutic index for seizure protection compared to CNS adverse effects (rotarod performance) was higher for levetiracetam compared to other AEDs. In rats and mice, levetiracetam produced moderate decreases in activity and hypotonia at oral or i.p. doses of 900 - 1800 mg/kg. Pharmacological effects on gastrointestinal, immune system, hematological effects, and renal function were minimal to none. It induced transient hemodynamic changes including increased pulmonary arterial pressure in dogs after i.v. injection.

The **mechanism of action** of levetiracetam has not yet been established. *In vitro* experiments, including ligand binding assays, demonstrated that levetiracetam does not interact with inhibitory and excitatory neurotransmission. However, a brain-specific and stereoselective binding site for the drug has been demonstrated to exist in plasma membranes from the central nervous system (CNS). In addition, in vitro and in vivo recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability.

Preclinical investigations of the **ADME** of levetiracetam in mice, rats, rabbits and dogs revealed rapid and complete absorption that is maintained over a large dose range. Levetiracetam was rapidly and evenly distributed throughout the body following single and repeated administration. The volume of distribution is approximately 0.5 to 0.7 L/kg. Levetiracetam is not significantly bound to plasma protein. Levetiracetam crosses the placental barrier and enters the CNS. Urinary excretion is the primary route of elimination, with at least 60% of an administered dose excreted as unchanged levetiracetam. Metabolic pathways include hydrolysis of the acetamide, hydroxylation of the 2-oxopyrrolidine and opening of the 2-oxopyrrolidine ring. Hydrolysis of the acetamide is an enzymatic process with broad tissue distribution, including blood cells. Levetiracetam and ucb L057 do not inhibit cytochrome P450 isoenzymes. There is no evidence for enantiomeric interconversion of levetiracetam (the S-enantiomer).

Toxicology studies of levetiracetam included single and repeat i.v. and oral dosing in mice, rats, and dogs. **Single dose studies** indicated low acute toxicity - lethality was only reached after i.v. dosing in these studies. Oral administration was not lethal (> 2000 mg/kg) and was associated with only transient clinical signs (emesis, salivation, tremors, decreased motor activity, ataxia, tachypnea, and side lying). In a later genotoxicity study in mice (the micronucleus test), lethality was reached at 10000 mg/kg p.o. In dogs, emesis was a dose-limiting effect. In **repeat dose studies**, administration of levetiracetam was well tolerated.

Mortality was observed only following i.v. administration of 900 mg/kg in rats. In general, clinical signs were minimal across studies and species with the most consistent observations being neuromuscular effects, salivation, and emesis in dogs. In the rodent only, treatment-related changes in the liver and kidney were reported. In the liver, a reversible increase in liver weight and hypertrophy of centrolobular hepatocytes were observed in both sexes in rats and mice without degenerative/necrotic or proliferative changes. EM studies revealed smooth ER proliferation. Centrolobular vacuolation associated with lipid deposition occurred in male rats and in mice. The liver lesions are considered to be adaptive. Kidney lesions consisting of hyaline droplet nephropathy and exacerbation of chronic progressive nephropathy was observed in male rats only - these changes are male rat-specific, associated with alpha-2-microglobulin accumulation in the proximal tubules that is not toxicologically relevant to man. There was no target organ identified in the dog. No lethality, organ failure or other irreversible toxicity was observed after long term oral treatment up to 1800 mg/kg/day in the rat, 960 mg/kg/day in the mouse and 1200 mg/kg/day in the dog. A study involving administration of ucb L060 (the R-enantiomer) indicates a low potential for toxicity in animals. **Segment I, II, and III reproductive toxicity studies** conducted in rats and/or rabbits and mice did not reveal any effect on parental reproductive parameters and peri- and post-natal development. In some studies fetal/litter weights were decreased and the incidence of retarded ossification parameters was increased at the highest dose tested. Levetiracetam was **not mutagenic** in an acceptable battery of studies, and was **not carcinogenic** in lifetime feeding studies in the mouse and the rat. A number of toxicology studies (acute, repeat dose, and genetic toxicology) were conducted with **metabolites ucb L060 and ucb L057**. Metabolite L060 is a minor metabolite in humans and animals and was considered for development as a drug to improve cognitive function, and is also a degradant in the manufacturing process. Metabolite L057 is the major metabolite in humans and animals - levels were increased in patients with impaired renal function. Genetic toxicology was negative for both metabolites. There were no adverse findings in repeat dose studies of L057. Findings for L060 were similar to those for levetiracetam (ucb L059).

Exposure Comparisons:

Useful comparative data is contained in the above tables:

1. Table 3 - Plasma Pharmacokinetic Parameters after a Single Dose of 54 mg/kg (page 8)
2. Table 6 - Plasma Pharmacokinetics of Levetiracetam as a Function of Single Oral Doses in the Rabbit (page 34)

3. Table 7 - Plasma Pharmacokinetics of Levetiracetam as a Function of Repeat Oral Dosing in Humans (page 34)

Also refer to **Table 8 (next page)** for an overall summary of dose and exposure comparisons.

Table 8: Maximal Doses and Systemic Exposure in Man and Animals

						Ratio animal/man (60 mg/kg)				
Species	Dose mg/kg/ day	Dose mg/m^2/ day	Cmax ug/ml	AUC ug.h/ ml	Cav ug/ml	Dose mg/kg/ day	Dose mg/m^2/ day	Cmax ug/ml	AUC ug.h/ml	Cav ug/ml
Man	20	680	20	273	11					
	60	2040	57	640	27					
General toxicity and carcinogenicity										
Mouse (a)	960	4800	-	1505	63	16	2.4		2.3	2.3
Rat (a)	1800	14400	1184 (b)	3840	160	30	7	21	6	6
Dog (c)	1200	25200	733	5776	241	20	12	13	9	9
Reproduction										
Rat (d)	1800	-	839	-		30	-	15		
Rat (e)	3600	-	1427	16502		60	-	25	26	
Rabbit (e)	1800	-	2352	20259		30		41	31	
Mouse (e)	3000	-	1211	-		50		21		

(a) admixed in diet
(b) gavage
(c) capsules
(d) fertility peri and post natal tox
(e) teratology

Location of reviews:
See attached reviews by L. Freed and B. Rosloff for most of the pharmacology, safety pharmacology, pharmacokinetics, toxicokinetics, single and repeat dose toxicology. See attached review by Aisar Atrakchi for genetic toxicology of the metabolites L060 and L057. This NDA review contains some pharmacology, some safety pharmacology, some pharmacokinetics, some toxicokinetics, all of the repeat dose studies with metabolites L060 and L057, carcinogenicity studies, parent compound genetic toxicology, reproductive toxicology, and immunotoxicology. See also the attached review by E. Fischer for additional reproductive toxicology.

Past Pharm/tox Issue Resolution:

Issues from previous pharmacology/toxicology reviews [redacted] have been addressed and resolved above in the appropriate sections of this NDA review. Briefly, the 3-month dog study was not a GLP study but was accepted as having been conducted "in the spirit of GLP," reports of cardiovascular safety studies were submitted and reviewed, there was no need to pursue the pathogenesis of the urine crystals noted at only one time point in one study in one sex of one species (female rats), a genetic toxicology study (E. coli WP2uvrA) was submitted in lieu of S. typhimurium test strain TA 102, plasma/bone marrow documentation of exposure in the mouse micronucleus test was not needed as abundant treatment and dose-related clinical signs were documented in the mice in this study, and the contaminated plates noted in the CHO/HGPRT study are a normal occurrence in any such study and were discarded and not read.

UCB informed the FDA (16 Jul 99) that the European Agency for the Evaluation of Medicinal Products (EMEA) had suspended the review of the licensing application for levetiracetam pending audits of the rat and mouse carcinogenicity studies. The primary reason for the audits was due to the presence of drug levels in the plasma of some of the untreated control animals. There were also a number of other minor problems and discrepancies noted by the reviewers and the auditors. *Please refer to pages 23-24 of this NDA review for a detailed discussion.* UCB informed the FDA (30 Sep 99) that the EMEA had lifted the suspension of their review following inspections and audits by the UK and Belgian GLP Monitoring Authorities of the contract laboratory which conducted the animal studies and of the analytical laboratory which analyzed the blood samples. The auditors determined that all studies had been conducted according to GLP with only minor deviations. The cause of detectable drug levels in the plasma in some of the control rats and mice was not determined, however it was believed that either diet contamination or plasma contamination had occurred. The FDA CAC concluded that this deficiency probably did not affect the outcomes of the studies due to the low levels of contamination and the small number of animals affected, as well as the clear lack of any positive tumor findings. Minor problems and discrepancies were addressed and corrected satisfactorily by the sponsor.

Current Toxicology Issues:
This reviewer disagrees with the conclusion of the Carcinogenicity Assessment Committee. Please refer to pages 16-18 of this review for a detailed discussion. The CAC accepted the rat study as a negative study, however rejected the mouse study. This reviewer disagrees with the CAC and accepts the mouse study. Despite its deficiencies, dose selection was appropriate and based upon the results of a 13-week study, though retrospective criticism is warranted due to the apparent lack of predictive power of the 13-week study for the 80-week study. The lack of any borderline or positive tumor findings in this study strengthens the acceptability of the study. The male part of the study was acceptable as a near-MTD was clearly achieved. The female part of the study could be repeated with higher doses, if the Division deems this appropriate, as the dose could have clearly been higher.

UCB, independently, not at the request or provocation by the EMEA or FDA, is conducting an independent peer review of the entire rat carcinogenicity study and will repeat the statistical tumor analysis (expected completion in November 1999).

Safety Evaluation:
The data summarized above indicates a low toxicity profile for this drug in animal models, and no significant safety concerns are predicted for human subjects based upon the animal data.

Labeling Review (NDA):
Proposed labeling is in Volume 1, Section 2. Pages 7-8 (Clinical Pharmacology) and page 20 (Carcinogenesis, Mutagenesis, Impairment of Fertility/Pregnancy). Labeling review of fertility and pregnancy by Ed Fisher is attached (attachment #1).

Recommended changes to sponsor's proposed package insert (Key to editing in red - deletions are indicated by strike-through, additions are italicized and underlined):

DRAFT LABELING

DRAFT

LABELING

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RECOMMENDATIONS:

Based upon the pharmacology and toxicology review, the NDA is approvable.

Changes to labeling are necessary - see section "Labeling Review" immediately above, and Attachment #1 from Ed Fisher.

Reviewer signature/team leader signature [Concurrence/Non-concurrence]
Jennifer A. Burris /S/ 28 Oct 99
Glenna Fitzgerald

cc: NDA 21,035
HFD-120 Div Files /S/ 11/4/99
HFD-120 Burris/Fitzgerald/Malandrucco/Freiman/Katz

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Draft date (#2): First draft 28 Sep 99, 2nd draft 27 Oct 99

Attachments:

#1. Reproductive Toxicology review/labeling review, PENDING, Ed Fisher
#2. Genetic Toxicology review (metabolites ucb 060/057), 22 Oct 99, Aisar Atrakchi

2 pages
REDACTED
DRAFT
LABELING

Attachment #2

NDA# 21-035
Drug: Levetiracetam Tabs
Sponsor: UCB Pharma Inc.,
1950 Lake Park Dr.
Smyrna, GA 30080
Rec. Date: Oct 20th 1999
Review date: Oct 22nd 1999
Reviewer: Aisar Atrakchi, Ph.D.
Team Leader: Glenna Fitzgerald, Ph.D.

GENETIC TOXICOLOGY

The following are assays conducted to assess the mutagenic potential of usb 060, an impurity in product manufacturing process and a human and animal metabolite.

Study title: Mouse lymphoma mutation assay/Agar method
Study# RRLE98B0501
Vol#, Page# 73/20085
Conducting lab: [redacted]
Date of Study Initiation/Completion: Aug 1997/Nov 1997
GLP Compliance: OECD/EC/FDA/Japanese compliant
QA Reports Yes (x) No ()
Drug Lot# Batch# 17
Study End point: gene mutation and clastogenicity (small and large colony sizing), in vitro assay. Colony sizing was done on the vehicle control and positive controls only since no cytotoxicity and no mutagenic responses were observed for the drug.

Methodology:
-Strain/Species/Cell line: L5178 mouse lymphoma cells.
-Dose selection Criteria:
- Basis of dose selection: toxicity assay in -/+S9.
- Range finding study: drug concentrations tested were: 0.5, 1.5, 5, 15, 50, 150, 500, 1500, and 5000ug/ml in single culture plates.
-Test Agent Stability: responsibility of sponsor.
-Metabolic Activation System: Aroclor 1254 induced liver S9 from male Fischer rats.
-Controls:
-Vehicle: water
-Negative Controls: not done
-Positive Controls: in –S9, 2 positive controls were tested: EMS 250ug/ml (large colony inducer) and MMS 15ug/ml (small colony inducer). In +S9 3MC at 2.5ug/ml was used, it induces both small and large colonies.

MLP ucb-L060 (Cont.)

-Exposure Conditions:

-Incubation and sampling times: all tests were done in -/+S9 and in duplicate except for the vehicle control which was tested in quadruplicate. Cultures were incubated with the drug for 4hrs and cells expressed for 2days.

-Doses used in definitive study: 2000, 3000, 4000, 5000ug/ml. A total of 4 assays was done, 2 in +S9 and 2 in – S9.

-Analysis:

-No. slides/plates/replicates/animals analyzed: duplicates for treated cultures and quadruplicates for the vehicle control.

-Counting method: the program used was an image analysis that also automatically measured colony sizing, it was referred to as the MLA program and details of mutant selection and colony size were provided. Histograms of the sizes were plotted and when possible, relative mutant fractions were calculated.

-cytotoxic endpoint: decrease in % RSG (relative suspension growth).

-Genetic Toxicity endpoint/results: increase in mutation frequency.

-Statistical methods: if a weakly positive or equivocal response is obtained, ANOVA and t-test will be used for confirmation. However, the sponsor stated that statistics will unlikely classify a response that accommodate the assay criteria, as non-significant.

-Criteria for Positive results: if cloning efficiency (CE) was at least 10% of the concurrent control and mutant frequency of the 2 cultures is at least 1.7x higher than the mean control value. The above criteria present in the highest concentration and preferrably an increase is seen in the other concentrations. Also, a concentration is positive when 2 of the 2 experiments were measured within the same activation condition and the cpd is positive if the following is seen: in the 1st experiment the drug was positive but did not meet the criteria due to lack of results from a toxic concentration and if the 2nd experiment done at narrower range of concentrations, showed an unequivocal response.

Results:

-Study validity: valid

-Study outcome: negative

Summary:

The drug was not cytotoxic in the range finding assay upto 5000ug/ml concentration. Therefore, 5000ug/ml was used as the top concentration in the main mutation assay. There was no increase in mutation frequency or effect on colony sizing upto the maximum recommended conentration of 5000ug/ml in either presence or absence of S9.

Ucb-L060 (Cont.)

Study title/study #: Mutagenic activity with Salmonella typhimurium TA1535, TA1537, TA98, TA100, and E.coli WP2uvrA/RRLE94B0403.
Vol#, Page#72/20021
Conducting lab: [redacted]
Date of Study Initiation/Completion: Aug 1997/Sep 1997
GLP Compliance: MHW Japanese, EC, FDA.
QA Reports Yes (x) No ()
Drug Batch#: 17
Study End point: gene mutation in bacteria.

Methodology:
-Strain/Species/Cell line: TA1535, TA1537, TA98, TA100, and E.coli WP2uvrA
-Dose selection Criteria:
- Basis of dose selection: cytotoxicity assay.
- Range finding study: toxicity preliminary assay done using TA100 in -/+ S9. Single plate with the following concentrations of L060 were tested: 0.1, 1, 10, 100, 1000, and 5000ug/plate.
-Test Agent Stability: responsibility of sponsor.
-Metabolic Activation System: Aroclor 1254-induced livers from male Fischer 344 rats.
-Controls:
-Vehicle: sterile pure water.
-Negative Controls: not done.
-Positive Controls: 2-AAN 0.5ug/plate, MMS 200ug/plate, ENNG 2&5ug/plate, 9-AA 80ug/plate, and 2-NF 1ug/plate. All positive controls except MMS were dissolved in DMSO, MMS was dissolved in water.
-Comments: none
-Exposure Conditions:
-Incubation and sampling times: 20min incubation and for colony expression, 2 days of incubation.
-Doses used in definitive study: 156.25, 312.5, 625, 1250, 2500, and 5000ug/plate for each of the 5 bacterial strains and E.coli. two independent gene mutation assays were done.
-Study design:
-Analysis:
-No. slides/plates/replicates/animals analyzed: triplicate plates for each strain in both absence and presence of S9.
-Counting method: Biotran III automated counter using max sensitivity i.e. colonies of 0.1mm or greater in diameter were counted.
-cytotoxic endpoint: reduction in background lawn.
-Genetic Toxicity endpoint/results: increase in number of revertant colonies over the vehicle control.
-Statistical methods: not done.

Bacterial Ames Gene mutation ucb-L060 (Cont.)

-Criteria for Positive results: for TA98, TA1535, TA1537, E.coli: at least doubling of mean of vehicle control values at any concentration of the drug. For TA100, at least 1.5x increase over the vehicle control. Dose related response, however, at high concentrations the following maybe applied: 1) toxicity to bacteria, 2)specific tox to mutants, 3)inhibition of cpd metabolizing enzymes where mutagens require metabolic activation by the liver. Also, for a positive response, the effect should be reproducible.

Results:
-Study validity: valid.
-Study outcome: Negative

Summary:

Ucb-060 in all bacterial strains and E.coli in presence and absence of S9 upto 5000ug/plate, did not increase the number of revertant colonies.

The following are assays to assess the mutagenic potential for ucb L057, a human metabolite that was significantly increased in patients with renal disease.

Study title/study #: Mutagenic activity of ucb L057 with Salmonella typhimurium TA1535, TA1537, TA98, TA100, and E.coli WP2uvrA/RRLE98B0401.
Vol#, Page# 71/19580
Conducting lab
Date of Study Initiation/Completion: Jun 1997/Jul 1997
GLP Compliance: MHW Japanese
QA Reports Yes (x) No ()
Drug Batch#: A005
Study End point: gene mutation in bacteria.

Methodology:
-Strain/Species/Cell line: TA1535, TA1537, TA98, TA100, and E.coli WP2uvrA
-Dose selection Criteria:
- Basis of dose selection: cytotoxicity assay.
- Range finding study: toxicity preliminary assay done using TA100 in -/+ S9.

Single plate with the following concentrations of ucb L057 were tested: 0.1, 1, 10, 100, 1000, and 5000ug/plate.
-Test Agent Stability: responsibility of sponsor.
-Metabolic Activation System: Aroclor 1254-induced livers from male Fischer 344 rats.
-Controls:
-Vehicle: sterile pure water.
-Negative Controls: not done.

Bacterial Ames Gene mutation ucb-L057 (Cont.)

-Positive Controls: 2-AAN 0.5ug/plate, MMS 200ug/plate, ENNG 2&5ug/plate, 9-AA 80ug/plate, and 2-NF 1ug/plate. All positive controls except MMS were dissolved in DMSO, MMS was dissolved in water.
-Exposure Conditions:
-Incubation and sampling times: 20min incubation and for colony expression, 2 days of incubation.
-Doses used in definitive study: 156.25, 312.5, 625, 1250, 2500, and 5000ug/plate for each of the 5 bacterial strains and E.coli. two independent gene mutation assays were done.
-Study design:
-Analysis:
-No. slides/plates/replicates/animals analyzed: triplicate plates for each strain in both absence and presence of S9.
-Counting method: [redacted] using max sensitivity i.e. colonies of 0.1mm or greater in diameter were counted.
-cytotoxic endpoint: reduction in background lawn.
-Genetic Toxicity endpoint/results: increase in number of revertant colonies over the vehicle control.
-Statistical methods: not done.

-Criteria for Positive results: for TA98, TA1535, TA1537, E.coli: at least doubling of mean of vehicle control values at any concentration of the drug. For TA100, at least 1.5x increase over the vehicle control. Dose related response, however, at high concentrations the following maybe applied: 1) toxicity to bacteria, 2)specific tox to mutants, 3)inhibition of cpd metabolizing enzymes where mutagens require metabolic activation by the liver. Also, for a positive response, the effect should be reproducible.

Results:
-Study validity: valid.
-Study outcome: Negative

Summary:

Ucb-L057 in all 5 bacterial strains and E.coli, in presence and absence of S9, and upto 5000ug/plate, did not increase the number of revertant colonies.

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UCB-L057 (Cont.)

Study title: Mouse lymphoma mutation assay of ucb-L057/Agar method
Study# RRLE98B0502
Vol#, Page# 71/19647
Conducting lab[redacted]
Date of Study Initiation/Completion: Jul 1997/Oct 1997
GLP Compliance: OECD/EC/FDA/Japanese compliant
QA Reports Yes (x) No ()
Drug Lot# Batch# A005
Study End point: gene mutation and clastogenicity (small and large colony sizing), in vitro assay. Colony sizing was done on the vehicle control and positive controls only since no cytotoxicity and no mutagenic responses were observed for the drug.

Methodology:
-Strain/Species/Cell line: L5178 mouse lymphoma cells.
-Dose selection Criteria:
- Basis of dose selection: toxicity assay in -/+S9.
- Range finding study: drug concentrations tested were: 0.2, 0.6, 2, 6, 20, 60, 200, 600 and 2000ug/ml in single culture plates.
-Test Agent Stability: responsibility of sponsor.
-Metabolic Activation System: Aroclor 1254 induced liver S9 from male Fischer rats.
-Controls:
-Vehicle: water for the cytotox assay and tissue culture medium for the main mutation assay.
-Negative Controls: not done
-Positive Controls: in –S9, 2 positive controls were tested: EMS 250ug/ml (large colony inducer) and MMS 15ug/ml (small colony inducer). In +S9 3MC at 2.5ug/ml was used, it induces both small and large colonies. EMS & 3MC were dissolved in DMSO and MMS was dissolved in water.

Comment: the sponsor stated that level of toxicity and the directly related level of response with MMS tends to vary with time, necessitating changing concentrations occasionally which was done in this assay.

-Exposure Conditions:
-Incubation and sampling times: all tests were done in -/+S9 and in duplicate except for the vehicle control which was tested in quadruplicate. Cultures were incubated with the drug for 4hrs and cells expressed for 2days.

MLP ucb-L057 (Cont.)

-Doses used in definitive study: total of 4 assays was done; 2 in presence and 2 in absence of S9. Concentrations were as follows:

Assay 1 / -S9:	125, 250, 500, 1000, 2000, 3000, 4000ug/ml
Assay 2/ +S9:	250, 500, 1000, 2000, 3000, 4000, 5000ug/ml
Assay 3/ -S9:	2000, 3000, 4000, 5000ug/ml
Assay 4/ +S9:	2000, 3000, 4000, 5000ug/ml

-Analysis:

-No. slides/plates/replicates/animals analyzed: duplicates for treated cultures and quadruplicates for the vehicle control.

-Counting method: the program used was an image analysis that also automatically measured colony sizing, it was referred to as the MLA program and details of mutant selection and colony size were provided. Histograms of the sizes were plotted and when possible, relative mutant fractions were calculated.

-cytotoxic endpoint: decrease in % RSG (relative suspension growth).

-Genetic Toxicity endpoint/results: increase in mutation frequency.

-Statistical methods: if a weakly positive or equivocal response is obtained, ANOVA and t-test will be used for confirmation. However, the sponsor stated that statistics will unlikely classify a response that accommodate the assay criteria, as non-significant.

-Criteria for Positive results: if cloning efficiency (CE) was at least 10% of the concurrent control and mutant frequency of the 2 cultures is at least 1.7x higher than the mean control value. The above criteria present in the highest concentration and preferrably an increase is seen in the other concentrations. Also, a concentration is positive when 2 of the 2 experiments were measured within the same activation condition and the cpd is positive if the following is seen: in the 1st experiment the drug was positive but did not meet the criteria due to lack of results from a toxic concentration and if the 2nd experiment done at narrower range of concentrations, showed an unequivocal response.

Results:

-Study validity. valid

-Study outcome: negative.

MLP ucb-L057 (Cont.)

Comment:

In the cytotoxicity assay, ucb-L057 was cytotoxic to cells causing complete lethality in –S9 and 70% reduction in RSG in +S9. It was noted that pH of the medium at this concentration as well as the next lower concentration of 600ug/ml, was decreased relative to that of the negative control:

		-S9	+S9
pH after 4hr	*vehicle control*	*7.45*	*7.35*
	600ug/ml	*7.15*	*7.01*
	2000ug/ml	*5.90*	*6.20*

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The sponsor indicated that excessive shifts in pH in mammalian cell assays, can cause false positives (Scott et al., 1991). Because of this, the vehicle was changed from water to tissue culture. iT is curious though that no such changes were observed in this assay when tested using the parent and ucb-060 metabolite.

Summary:

The ucb-L057 was cytotoxic causing cell lethality at 2000ug/ml when water was used as the vehicle control in the cytotox assay. This cell toxicity was contributed to the excessive shift in pH at the 2000ug/ml and less marked shift occurred at 600ug/ml. The vehicle was changed to tissue culture medium in the main mutation assays and pH was closely monitored in the 1st of 4 assays. No changes were seen and pH was not monitored in the remaining 3 of the 4 main assays. Note that such shifts in pH were not observed in this assay when the parent, ucb-L059 and the metabolite ucb-L060 were tested. The top concentration tested in the main assay was 5000ug/ml. There was no increase in mutation frequency upto the maximum conentration tested of 5000ug/ml in either presence or absence of S9.

APPEARS THIS WAY
ON ORIGINAL

cc.
/Div File NDA# 21-035
/G. Fitzgerald/J. Burris/A. Atrakchi/M. Malandrucco

Executive CAC
21 September 1999

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Andrea Weir, Alternate Member
Glenna Fitzgerald, Team Leader
Jennifer A. Burris, Presenting Reviewer

Author of Minutes: JA Burris

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21-035
Drug Name: levitiracetam
Sponsor: UCB Pharma Inc.

Mouse Carcinogenicity Study
80 week study ('89-'91); dose levels 60, 240, and 960 mg/kg admixed in diet. The committee discussed a number of study deficiencies, including the short duration, presence of drug contamination in control animal diet, and the lack of significant body weight reduction or toxicity in the high dose group. The committee agreed that there was no appropriate basis for dose selection i.e. an MTD was not achieved, body weights were not significantly reduced, no toxic endpoints were evident, exposures only exceeded that in humans by 2-5X. In addition, by current standards the study should have been extended to 104 weeks as survival was good at week 80.

Rat Carcinogenicity Study
104 week study ('89-'91); dose levels 50, 300, and 1800 mg/kg admixed in diet. The committee discussed a number of study deficiencies. These included drug contamination of control animal diet, large body weight reductions in the mid and high dose groups (↓20% and 30% respectively) with increased survival and without toxicity, and findings of the UK GLP audit, particularly missing tissue samples. The dramatic reductions in body weight in the mid and high dose groups accompanied by reduced food consumption (↓5 and 10% in mid and high dose males; ↓5% in high dose females) were a major concern to the committee. Gavage studies at similar doses did not affect body weight or food consumption in studies up to 52-weeks (see CAC report addendum). This suggests that the loss of body weight with decreased feed intake in this drug-in-diet carcinogenicity study may have been due to reduced palatability. However, in a 26-week drug-in-diet study at similar doses, there was a loss of body weight without decreased food consumption indicating no palatability problem. The committee agreed that a more appropriate route of administration in this carcinogenicity study would have been by gavage. Despite a possible palatability problem, the toxicokinetic data demonstrated that increasing doses resulted in increased exposure, though less than a linear relationship. For example, at 102 weeks, rat AUCs were 275, 1158, and 3864 ug.h/mL respectively at the doses 50, 300, and 1800mg/kg; dose ratios were 1.0, 6.0, 36 and AUC ratios 1.0, 4.2, 14.1. The committee noted that exposures

in the highest dose in the rat study relative to human therapeutic doses were only 4-6X. In the rat low dose group, rat exposures relative to human were only 0.5-1.0X.

Executive CAC Recommendations and Conclusions:
The occurrence of control diet contamination in both studies was a concern. However, the very low levels of contamination and the small number of animals affected, as well as the clear lack of any positive tumor findings in both studies, lead the committee to conclude that this deficiency probably did not affect the outcomes of the studies.

The committee agreed that the mouse study was unacceptable, despite negative tumor findings, primarily because there was no appropriate basis for dose selection.

The committee agreed that the rat study is acceptable as a negative study pending any additional information from an ongoing European audit of UCB Pharma's analytical research facility in Belgium and an ongoing pathology peer review. There were no positive tumor findings, however the mid and high dose groups had increased survival, greatly reduced body weights, and decreased feed consumption possibly due to poor palatability (although see supervisory note in appended report). Gavage would have been the preferred route of administration because gavage studies, as opposed to drug-in-diet studies, did not affect body weight, and higher exposures may have been achievable.

/S/ 10/4/99

Joseph D. George, Ph.D.
Chair, Executive CAC

cc:

Division File, HFD HFD-120
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ADDENDUM to CAC Report 21 Sep 99 NDA 21-035 J.A. Burris

ORAL STUDIES IN THE RAT with Levitiracetam – Effects on Body Weight and Food Consumption

A. Studies with drug admixed in the diet
1. Palatability study in rats by dietary administration for one month (English translation LE89C082, vol 30). SD rats dosed via continuos feeding admixed in the diet at 0, 22 67, 200, 600, and 1800 mg/kg/day. 9/sex/group. No effects on food consumption. Slight decrease in body

weights in both sexes at 1800 mg/kg/day in the later half of the study, though not statistically significant. Age at initiation of diet: 7-9 weeks. Study report concluded that the admixture of compound in the diet did not inhibit food intake/body weight gain.
2. 26-week toxicity study by repeated oral dosing (admixed with diet) with compound ucb L059 in the rat (RRLE91H1301 Vol. 34). SD rats, 21/sex/group, doses 0, 50, 160, 520, 1700 mg/kg/day. Body weights decreased in 520 and 1700 mg/kg males (6% and 10% respectively) and in the 1700 mg/kg females (10%). No consistent effects on food consumption.
3. Two year carcinogenicity study in SD rats (UCB 292/91989). Doses at 50, 300, and 1800 mg/kg/day. Body weights greatly reduced throughout the study in both sexes at 300 and 1800 mg/kg (20% and 30% respectively). Food consumption reduced in both sexes at 1800 mg/kg (5% in females, 10% in males) and in males at 300 mg/kg (5%).

B. Studies by oral gavage
1. Three month study in SD rats by gavage (report LE86L201, vol. 31) at 200, 600, and 1800 mg/kg/day. Body weights and food consumption slightly decreased in HDF without statistical significance.
2. (UCB #227/87415) 52-week toxicity in rats by oral gavage.
70, 350, and 1800 mg/kg/day. No effects body weights, food consumption.

Summary:

By **gavage** at doses similar to those used in the carcinogenicity study:
° 52 week study - no effects on body weight or food consumption
° 3-month study - minimal decrease in body weight and food consumption (HDF only)
By **admixture in the diet** at doses similar to those used in the carcinogenicity study:
°1-month study - minimal decrease in body weight (HDM&F), normal food consumption
° 26-week study -significant body weight reductions in HDM&F and MDM with no decreases in food consumption in
° 2-year study - significant body weight reductions in MD and HD both sexes with significant decreases in food consumption in HD M&F and MDM

Conclusions: The lack of adverse effects on body weight and food consumption in gavage studies versus the presence of these effects in the drug-in-diet carcinogenicity study suggests that there may have been a palatability problem in the higher dose groups.

Supervisory note: The gavage studies call into question the source of the body weight effects in the carcinogenicity study as being related to drug palatability rather than toxicity. However, the absence of an effect on food consumption or body weight in the 1-month dietary admixture study, where palatability generally tends to be more predominant, decreases this concern. Also, palatability was not a problem in the 26-week dietary admixture study, in which decreases in body weight were not accompanied by decreased food consumption.

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