CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-505

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-505
Generic Name:	Levetiracetam 100 mg/mL Oral Solution
Brand Name:	Keppra®
Sponsor:	UCB Pharma
Indication:	Adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy
OND Clinical Division:	Division of Neuropharmacologic Drug Products (HFD-120)
OCPB Division:	Division of Pharmaceutical Evaluation 1 (HFD-860)
Submission Type:	Standard (New Formulation)
Submission Date:	6/19/02, 9/13/02
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

Executive Summary

Synopsis: The sponsor is seeking approval to market a new formulation of levetiracetam, Keppra® oral solution 100 mg/mL, for adjunctive therapy in the treatment of partial onset seizures, in adults with epilepsy. Keppra® is already available commercially as 250 mg, 500 mg, 750 mg tablets. Keppra tablets are approved for the same indication that is being sought by the sponsor for the oral solution. The recommended dose range is 1000 to 3000 mg/day administered in two divided doses. The new oral solution is proposed to be an alternative for adult patients who have difficulty in swallowing tablets. The sponsor is requesting deferral of pediatric studies for all pediatric groups in this submission. The sponsor stated that [redacted] The application contains a pivotal study that evaluated whether the proposed Keppra oral solution is bioequivalent to the approved Keppra tablets.

Levetiracetam (ucb L059) is the S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide. Levetiracetam is rapidly and completely absorbed after oral administration. After oral administration, peak plasma levels and AUCs are proportional and indicate linearity of exposure up to 5000 mg. Neither levetiracetam nor its inactive metabolite (ucb L057) is extensively bound to plasma proteins. Following oral administration of radioactive drug, the two major radioactive components in urine were levetiracetam and ucb L057, an acidic metabolite obtained by hydrolysis of the acetamide group; these were present as 65.9% and 23.7% of the dose, respectively. The hydrolysis of levetiracetam is mediated by broadly distributed serine esterase(s) distinct from well characterized cholinesterase and carboxylesterase enzymes. The plasma half-life of levetiracetam in adult healthy volunteers was 7 hours. In vitro assays demonstrated that ucb L057 production is not supported by hepatic cytochrome P450 isoforms.

The application for the tablet formulation (NDA 21-035) and the clinical pharmacology and biopharmaceutics review of that NDA indicated that there is no significant effect of food on the extent of absorption of the drug. Consistent with the minimal hepatic metabolism and the urinary profile of excretion, data analysis of possible drug-drug interaction (levetiracetam with phenytoin, oral contraceptives, digoxin, warfarin, probenecid, and valproate) in NDA 21-035 did not identify any pharmacokinetic interactions with levetiracetam.

Levetiracetam 750 mg administered as a 10% oral solution was demonstrated to be bioequivalent to levetiracetam administered as a 750 mg tablet (highest strength) following single oral doses in 24 fasting healthy subjects. The 90% confidence interval (CI) for the geometric mean ratios of AUC and Cmax for the two treatments were between 0.80 and 1.25. The solution formulation used in the pivotal bioequivalence study (Study N1072) is identical to the proposed solution commercial formulation and was produced at the proposed commercial site.

Multiple dose co-administration of valproic acid 500 mg twice daily did not significantly alter the extent and rate of exposure of levetiracetam when given in combination. The cumulative urinary excretion of levetiracetam and its major metabolite were also not significantly altered when administered in combination with valproic acid compared to the parameter values obtained for levetiracetam, when it was given alone.

Recommendation: Based on the data submitted to the Human Pharmacokinetics and Bioavailability section of NDA 21-505 to fulfill section 320 and 201.5 of 21CFR, equal doses of Keppra® oral solution (100 mg/mL; 750 mg) and tablet (750 mg) have been demonstrated to be bioquivalent. Hence, Keppra® oral solution (100 mg/mL) is recommended for approval.

Labeling Recommendations

The following additions to the Pharmacokinetic and drug interaction sections of the approved label for levetiracetam tablets are proposed by the sponsor. Additions are double underlined and *Reviewer comments are in italics*

Pharmacokinetics

Overview
Levetiracetam is rapidly and almost completely absorbed after oral administration. Levetiracetam tablets and oral solution are bioequivalent. ...

Reviewer comment: Addition is acceptable

Absorption and Distribution
Absorption of levetiracetam is rapid, with peak plasma concentrations occurring in about an hour following oral administration in fasted subjects. The oral bioavailability of levetiracetam tablets is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption. ...

Reviewer comment: Addition is acceptable

Pharmacokinetic Interactions

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).

Reviewer's comments: Addition is acceptable.

Precautions

Drug Interactions

Valproate

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.

Reviewer's comment: Addition is acceptable.

/S/

Kofi A. Kumi, Ph.D.

/S/

RD/FT Initialed by Raman Baweja, Ph.D.

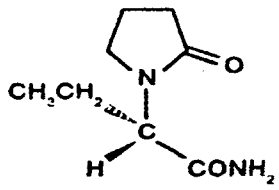
CC: NDA 21-505, HFD-120, HFD-860 (Mehta, Sahajwalla, Baweja, Kumi), Central Document Room (Biopharm – CDR)

Table of Contents

	Page
Executive	01
Synopsis	01
Recommendations	02
Labeling Recommendations	02
Question Based Review	
General Attributes	05
Pivotal Bioequivalence	06
Interaction between levetiracetam and valproate	08
Analytical method validation	12
Appendix	
Individual Study Reviews	13

What are the general attributes of levetiracetam?

Levetiracetam is an antiepileptic drug (AED). Levetiracetam is a pyrrolidone derivative and is chemically designated (S)-alpha-ethyl-2-oxo-1- pyrrolidone acetamide and has a molecular weight of 170.21 and molecular formula of $C_{18}H_{14}N_2O_2$. Its water solubility is 1.04 g/mL and the partition coefficient (octanol/water) is 0.64 ± 0.02. The chemical structure is as follows:



Levetiracetam is rapidly and almost completely absorbed after oral administration. Peak plasma concentration (Cmax) is generally reached about 1 hour after dosing in fasting subjects. Absolute bioavailability is reported to be close to 100% when levetiracetam is administered as capsules. The commercial tablets were demonstrated to be bioequivalent to the capsules in terms of the extent and rate of their absorption. There is no significant effect of food on the extent of absorption of levetiracetam. After oral administration, peak plasma levels and AUCs were reported to be proportional to doses up to 5000 mg. Neither levetiracetam nor its major metabolite, ucb L057, is extensively bound to plasma proteins. The volume of distribution (Vd) of levetiracetam is in the range of 0.5 to 0.7 L/kg. Following oral administration of radioactive drug, the two major radioactive components in urine were levetiracetam and ucb L057, an inactive acidic metabolite obtained by hydrolysis of the acetamide group; these were present as 65.9% and 23.7% of the dose, respectively. The hydrolysis of levetiracetam is mediated by broadly distributed serine esterase(s) distinct from well characterized cholinesterase and carboxylesterase enzymes. In vitro assays demonstrated that ucb L057 production is not supported by hepatic cytochrome P450 isoforms. The plasma half-life of levetiracetam in adult healthy volunteers was 7 hours. Half-life does not vary with dose, the route of administration, or after multiple dosing. Levetiracetam (Keppra®) is already available commercially as 250 mg, 500 mg, 750 mg tablets. The typical commercial batch size for the proposed oral solution is [redacted] The formulation used in the pivotal bioavailability study (N01072) is identical to the proposed commercial oral solution formulation and was produced at the proposed commercial site. The batch size was [redacted] The following tables contain the formulation for the approved tablet and the proposed oral solution

COMPONENT	15 ml typical dose		16 oz bottle (475 ml)	batch
	(mg)	(mg)	(mg)	(kg)
Levetiracetam	1500.0		47500	
Purified Water, USP				
Methylparaben, NF				
Propylparaben, NF				
Glycerin, USP				
Ammonium Glycyrrhizinate				
Sodium Citrate Dihydrate, USP				
Citric Acid Monohydrate, USP				
Potassium Acesulfame, EP				
Maltitol Solution, NF (Lycasin 80-55)				
Grape Flavor				

Table 1: Typical Batch Formula for Keppra Oral Solution (above)

Table 2: Composition of Commercial Levetiracetam Tablets

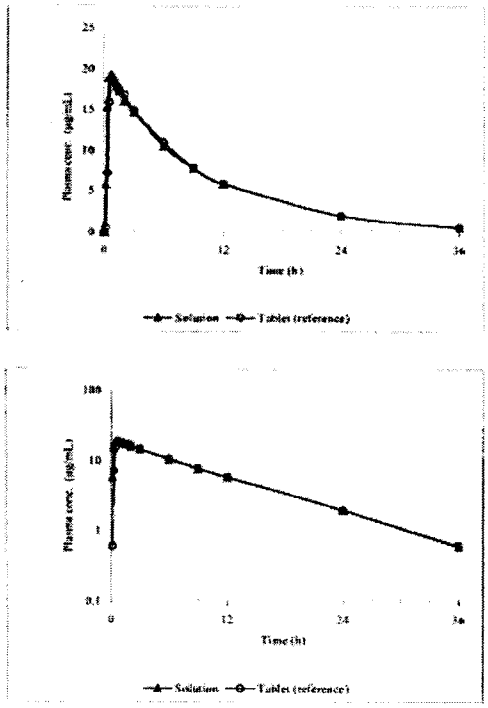
Component	250 mg tablet	500 mg tablet	750 mg tablet
	Weight (mg)		
Levetiracetam	250.0	500.0	750.0
Corn starch, NF			
Povidone, NF			
Talc, USP			
Colloidal silicon dioxide, NF			
Magnesium Stearate			
	blue)	yellow)	
Total Weight	335.0	670.0	1005.0

Is the proposed oral solution bioequivalent to the approved tablet?

Levetiracetam 750 mg administered as a 10% oral solution was demonstrated to be equivalent to levetiracetam administered as a 750 mg tablet following single oral doses in fasting healthy subjects. The 90% confidence interval (CI) for the geometric mean ratios of AUC and Cmax for the two treatments were between 0.80 and 1.25.

The submission contained a study that evaluated single dose bioavailability and bioequivalence of Levetiracetam given as either 7.5 mL (750 mg) of a 10% oral solution or as 750 mg tablets in 24 healthy fasting volunteers. This was a single center, open-label, two-way crossover, single dose study. The study population consisted of 24 healthy male and female volunteers aged 18 to 55 years. Each subject was randomized to receive a single oral dose of the oral solution (7.5 mL containing 750 mg of levetiracetam) or a single oral dose of the tablet (1 x 750 mg tablet) on day 1 and a single oral dose of the alternate formulation on Day 8. The treatment periods were separated by a washout period of 7 days. Blood samples were obtained at specified time periods.

The mean plasma concentration by time curves for the solution and the tablet formulations were essentially superimposable (Figure 1). Mean values for derived PK parameters were comparable for the two formulations as shown in Table 3. The assessment of bioequivalence based on Ln-transformed data for AUC, AUC(0-t), and Cmax is summarized in Table 4. The 90% confidence intervals for each of these pharmacokinetic variables were within, the regulatory bioequivalence criteria of 80 – 125%.



[a] Data are expressed as mean, n=24 in lin-lin scale (top) and in log-lin scale (bottom)

Figure 1: Mean Plasma Concentration-Time Profile of Levetiracetam in Healthy Volunteers Following a Single Administration of Levetiracetam Given Either as 7.5 mL (750 mg) of a 10% Oral Solution or a 750 mg Tablets (reference)

Parameters		Mean [a] ± SD	
		Solution N=24	Tablet N=24
AUC	(µg • h/mL)	201.7 ± 33.6	204.7 ± 33.6
$AUC_{(0-t)}$	(µg • h/mL)	193.0 ± 35.3	195.2 ± 35.0
C_{max}	(µg / mL)	21.1 ± 4.0	20.3 ± 3.9
t_{max}	(h)	0.50 (0.33, 1.50)[b]	0.75 (0.50, 2.00)[b]
MRT	(h)	10.3 ± 1.20	10.6 ± 1.46
λ_z	(1/h)	0.0955 ± 0.0119	0.0953 ± 0.0135
$t_{1/2}$	(h)	7.4 ± 0.87	7.4 ± 1.02
CL/f	(L/h)	3.8 ± 0.61	3.8 ± 0.61
	(mL/min)	63.6 ± 10.2	62.6 ± 10.2
CL/f/WT	(mL/min/kg)	0.86 ± 0.14	0.85 ± 0.15
nCL/f	(mL/min/1.73m²)	58.7 ± 7.5	57.9 ± 8.1
V_z/f	(L)	40.7 ± 8.9	40.3 ± 8.9
V_z/f/WT	(L/kg)	0.54 ± 0.08	0.54 ± 0.08

[a] Arithmetic mean.
[b] Median (range).

Table 3 (above): Pharmacokinetic Parameters of Levetiracetam in Healthy Volunteers Following a Single Oral Dose of Levetiracetam Given Either as 7.5 mL (750 mg) of a 10% Oral Solution or a 750 mg Tablet

		Solution (N=24)	Tablet (N=24)	Formulation Comparison[a]	90% CI[b]
Natural Log-Transformed Data					
AUC µg • h/mL	Mean[c] 95% CI[d]	199.08 [185.51, 213.64]	202.11 [188.33, 216.89]	98.50	[96.60, 100.45]
$AUC_{(0-t)}$ µg • h/mL	Mean[c] 95% CI[d]	189.96 [175.70, 205.39]	192.20 [177.77, 207.81]	98.83	[96.60, 101.12]
C_{max} µg / mL	Mean[c] 95% CI[d]	20.70 [19.06, 22.48]	19.95 [18.36, 21.66]	103.78	[98.92, 108.87]

[a] Ratio (solution/tablet) of the treatments.
[b] The 90% confidence interval for the ratio of the treatments.
[c] Geometric mean = antilogarithm of the least squares mean from the ANOVA on log transformed data.
[d] The 95% confidence interval for the mean.

Table 4 (above): Parametric Analyses for AUC, AUC(0-t) and Cmax Following a Single Oral Dose Levetiracetam Given Either as 7.5 mL (750 mg) of an Oral Solution or a 750 mg Tablet to Healthy Volunteers

Is there a clinically relevant pharmacokinetic interaction between levetiracetam and valproate?

Multiple-dose co-administration of VPA 500 mg bid did not significantly alter the pharmacokinetics of levetiracetam. The 90% CI was within 80 to 125. The cumulative urinary excretion of levetiracetam and its major metabolite were also not significantly altered when administered in combination compared to the parameter values obtained for levetiracetam, when levetiracetam was given alone.

In the original application (NDA 21-035) for the tablet formulation, a meta- analysis of data from studies in epileptic patients evaluating the possible interaction of levetiracetam with anti-epileptic drugs indicated that valproic acid pharmacokinetics are not altered by co-administering with levetiracetam

The submission contained a study that assessed the effect of valproate steady state administration on the single dose pharmacokinetics of Levetiracetam in healthy volunteers. The study was an open-label, single dose, one-way sequence cross over study. Sixteen healthy volunteers between the ages of 18 to 55 years were enrolled. A single dose of 1500 mg levetiracetam was taken orally on day 1 in the morning. From day 3 to 11, VPA (500 mg b.i.d. orally) was administered to reach steady state plasma levels from day 10 onwards. A single dose of 1500 mg levetiracetam was taken again on day 10 in the morning. A multipoint pharmacokinetic profile was performed for levetiracetam and its major metabolite ucb L057 from day 1 to 3 (alone) and from day 10 to 12 (combination). Blood samples for analyses of levetiracetam and L057 concentrations were collected at specified time periods. Blood samples were collected for plasma analyses of trough levels of VPA before 2, 5, 9, 13 and 15th dose of VPA.

The mean pharmacokinetic profiles for levetiracetam (ucb L059) and its major metabolite, ucb L057 are provided in figure 2. The mean pharmacokinetic parameters for levetiracetam (ucb L059) and its metabolite (ucb L057) when levetiracetam is administered alone and with VPA are provided in the following tables (Tables 5 and 6)

Table 5: Pharmacokinetic parameters of Levetiracetam (ucb L059) after administration of a 1500 mg single oral dose of Levetiracetam either alone or with valproate

Pharmacokinetic Parameter	Unit	Levetiracetam alone	Levetiracetam with VPA	Ratio of geometric mean* (90% CI)
		Mean ± SD		
Cmax	µg/mL	39.6 ± 9.9	41.4 ± 9.7	104.7 (95.9,114.4)
Tmax[a]	h	0.67 (0.33 – 2.0)	0.67 (0.33-2.0)	0.00 (-0.29,0.13)[b]
λz	1/h	0.095 ± 0.014	0.094 ± 0.012	99.2 (97.6,100.7)
AUC	µg*h/mL	400 ± 47	397 ± 60	98.9 (96.2,101.6)
CL/F	mL/min/kg	0.89 ± 0.11	0.90 ± 0.13	101.1 (98.4,103.9)
Vz/F	L/kg	0.57 ± 0.07	0.58 ± 0.08	101.8 (99.4,104.3)
Ae	mg	939 ± 85	871 ± 113	92.9 (89.1,97.0)
fe	%	62.6	58.1 ± 7.6	

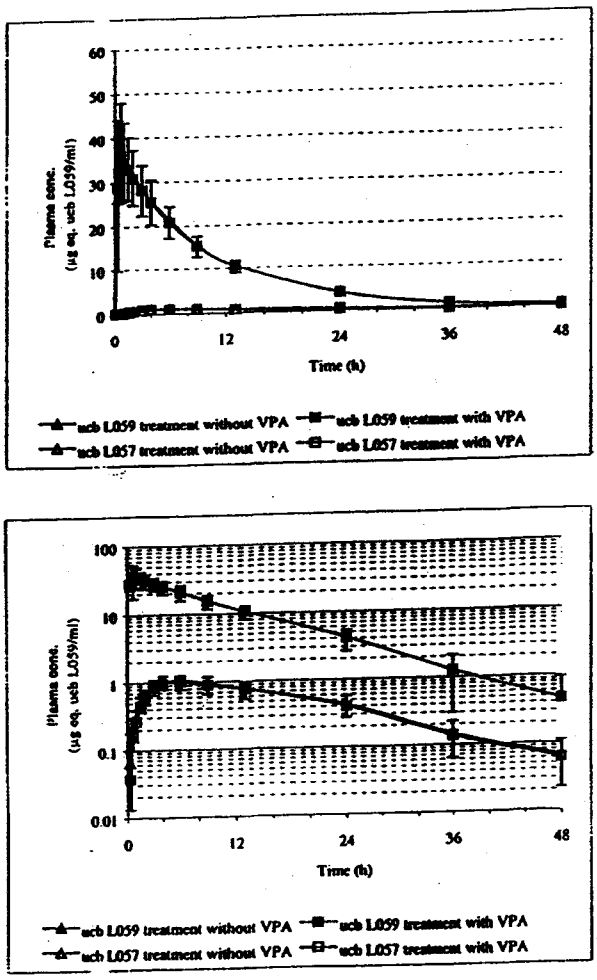
[a]Cmax, peak plasma concentration; tmax, time to reach Cmax; AUC, area under the plasma concentration-time curve extrapolated at infinite time; λz, terminal rate constant; Cl/f, apparent plasma clearance; Vz/f, volume of distribution; Ae and fe, cumulative amount excreted in urine over 48 hours in mg and % of the dose, respectively. [a]Median (min-max). [b]Median difference between test and reference and 90% CI of difference. *Computed from back transformation of the difference of least square means between test (co-administration with VPA) and reference (levetiracetam alone) treatment

Table 6: Pharmacokinetic parameters of ucb L057 after administration of a 1500 mg single oral dose of Levetiracetam either alone or with valproate

Pharmacokinetic Parameter	Unit	Levetiracetam alone	Levetiracetam with VPA	Ratio of geometric mean (90% CI)
		Mean ± SD		
Cmax	µg-eq/mL	1.08 ±0.20	1.02 ± 0.22	94.1 (89.8,98.6)
Tmax[a]	h	6 (3 – 9)	6 (3- 9)	1.00 (0.00,1.50)
λz	1/h	0.082 ± 0.011	0.082± 0.011	100 (97.4,102.8)
AUC	µg-eq*h/mL	23 ± 6.5	21.9 ± 6.3	95.0 (90.3,99.9)
CL/F	mL/min/kg	0.89 ± 0.11	0.90 ± 0.13	101.1 (98.4,103.9)
Ae	mg-eq	308 ± 75	275 ± 58	87.9 (84.7,91.3)
fe	%	20.5 ± 5.0	18.3 ± 3.9	-

[a]Cmax, peak plasma concentration; tmax, time to reach Cmax; AUC, area under the plasma concentration-time curve extrapolated at infinite time; λz, terminal rate constant; Cl/f, apparent plasma clearance; Ae and fe, cumulative amount excreted in urine over 48 hours in mg and % of the dose, respectively. [a]Median (min-max). [b]Median difference between test and reference and 90% CI of difference. *Computed from back transformation of the difference of least square means between test (co-administration with VPA) and reference (levetiracetam alone) treatment

Detailed plasma data



Plasma concentrations-time profile of ucb L059 and ucb L057 in male and female healthy volunteers following a single oral administration of ucb L059 at a target dose of 1500 mg either alone or in co-treatment with valproic acid.
Data are presented as mean±SD (n=16), in lin-lin (top) and log-lin (bottom) scale.

Figure 2 (above)

When levetiracetam was given alone, the peak concentration was achieved at 0.67 hours. Concentrations then declined with a half-life of 7.5 ± 1.1 hours. The 48-hour cumulative urinary excretion of levetiracetam was equivalent to 62.6 ± 5.7% of the given dose. The renal clearance of levetiracetam was 0.58 ± 0.09 ml/min/kg.

Is the analytical method used in determination of levetiracetam concentrations acceptable?

The validation of the analytical method used in the determination levetiracetam and its metabolite, ucb L057, concentrations was submitted and reviewed under the application for levetiracetam tablets (NDA 21-035) and found acceptable. Validation and in process controls of the analytical method used in the determination of levetiracetam in the current studies are acceptable.

Plasma was analyzed for levetiracetam by extraction with methanol and using a [redacted]
Concentrations were quantitated using the ratio to an internal standard, and the assay was found to be linear, precise, and accurate over a plasma concentration range of [redacted] plasma. The lower limit of quantitation was generally [redacted] The sensitivity of the assay was increased by using a [redacted] A similar method was adapted for analysis of urine samples. The analytical method for the major metabolite, ucb L057 in plasma and in urine has also been validated. The analytical procedure used a liquid [redacted]

APPEARS THIS WAY
ON ORIGINAL

Appendix

Individual Study Reports

Study Title (N01072): A Randomized, Single Center, Open-Label, Two-Way Crossover Single Dose Bioavailability and Bioequivalence Study of Levetiracetam Given as Either 7.5 mL (750 mg) of a 10% Oral solution or as 750 mg Tablets in 24 Healthy Fasting Male and Female Subjects Aged 18 to 55 Years Inclusive (RRCE01L2002)

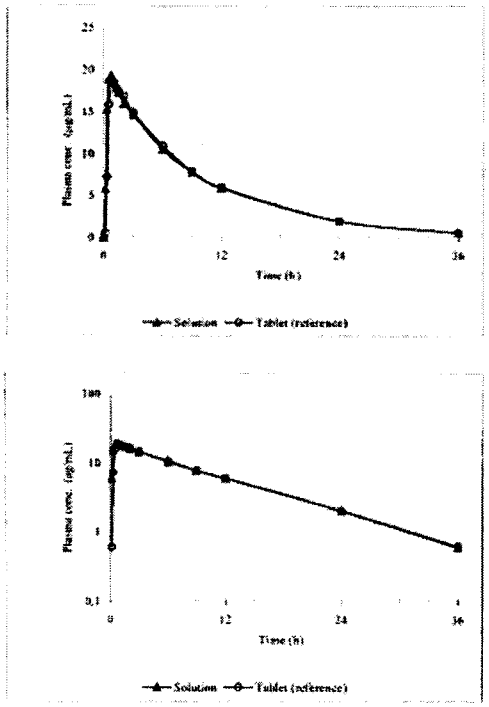
Objective: The primary objectives were: 1) To establish the systemic exposure profile of 750 mg levetiracetam oral solution in adults, 2) To compare the systemic exposure [Bioavailability (BA) / Bioequivalence (BE)] between 750 mg levetiracetam oral solution and the marketed 750 mg tablets (reference) in adults.
The secondary objective was to gain additional information on the safety of both levetiracetam formulations.

Study Design: This was a single center, open-label, two-way crossover, single dose bioavailability and bioequivalence study. The study population consisted of 24 healthy male and female volunteers aged 18 to 55 years. Each subject was randomized to receive a single oral dose of the oral solution (7.5 mL containing 750 mg of levetiracetam) or a single oral dose of the tablet (1 x 750 mg tablet) on Day 1 and a single oral dose of the alternate formulation on Day 8. After fasting overnight for 10 hours, the assigned formulation was taken with 240 mL of water. The treatment period were separated by a washout period of 7 days. The test product was levetiracetam 10 % oral solution, and the reference product was levetiracetam 750 mg tablets. Batch numbers were UKS0001-ST for the oral solution and 10209 for the tablets. Blood samples were obtained at any time in the morning prior to dosing; then, 10, 20, 30, 45, 60, 75, and 90 minutes after dosing; and 2, 3, 6, 9, 12, 24, and 36 hours after dosing.

Analytical Method: Levetiracetam was measured in plasma samples by a [redacted]. Calibration curves ranging from [redacted] were prepared in human plasma and used. The limit of quantitation was [redacted] The precision of the assay was less than [redacted] The mean of daily recoveries of levetiracetam in QC samples analyzed within the study were 96.4, 96.1 and 94.1% at nominal concentrations of [redacted], respectively.

Data Analysis: Pharmacokinetic (PK) parameters were computed from plasma concentration - time profiles following single oral doses of the two formulations by non-compartmental methods.

Results: The mean plasma concentration by time curves for the solution and the tablet formulations were essentially superimposable (Figure 1). Mean values for derived PK parameters were comparable for the two formulations as shown in Table 1. Although the median tmax was observed earlier for the solution (0.50 h) than for the tablet (0.75 h), this difference was not statistically significant. The assessment of bioequivalence based on Ln-transformed data for AUC, AUC(0-t), and Cmax is summarized in Table 2. The 90% confidence intervals for each of these pharmacokinetic variables were within, the regulatory bioequivalence criteria of 80 – 125%.



[a] Data are expressed as mean, n=24 in lin-lin scale (top) and in log-lin scale (bottom)

Figure 1: Mean Plasma Concentration-Time Profile of Levetiracetam in Healthy Volunteers Following a Single Administration of Levetiracetam Given Either as 7.5 mL (750 mg) of a 10% Oral Solution or a 750 mg Tablets (reference)

Parameters		Mean [a] ± SD	
		Solution N=24	Tablet N=24
AUC	(µg • h/mL)	201.7 ± 33.6	204.7 ± 33.6
$AUC_{t(t)}$	(µg • h/mL)	193.0 ± 35.3	195.2 ± 35.0
C_{max}	(µg / mL)	21.1 ± 4.0	20.3 ± 3.9
t_{max}	(h)	0.50 (0.33, 1.50)[b]	0.75 (0.50, 2.00)[b]
MRT	(h)	10.3 ± 1.20	10.6 ± 1.46
λ_z	(1/h)	0.0955 ± 0.0119	0.0953 ± 0.0135
$t_{1/2}$	(h)	7.4 ± 0.87	7.4 ± 1.02
CL/f	(L/h)	3.8 ± 0.61	3.8 ± 0.61
	(mL/min)	63.6 ± 10.2	62.6 ± 10.2
CL/f/WT	(mL/min/kg)	0.86 ± 0.14	0.85 ± 0.15
nCL/f	(mL/min/1.73m²)	58.7 ± 7.5	57.9 ± 8.1
V_z/f	(L)	40.7 ± 8.9	40.3 ± 8.9
V_z/f/WT	(L/kg)	0.54 ± 0.08	0.54 ± 0.08

[a] Arithmetic mean
[b] Median (range).

Table 1: Pharmacokinetic Parameters of Levetiracetam in Healthy Volunteers Following a Single Oral Dose of Levetiracetam Given Either as 7.5 mL (750 mg) of a 10% Oral Solution or a 750 mg Tablet

		Solution (N=24)	Tablet (N=24)	Formulation Comparison[a]	90% CI[b]
Natural Log-Transformed Data					
AUC	Mean[c]	199.08	202.11	98.50	[96.60,
µg • h/mL	95% CI[d]	[185.51, 213.64]	[188.33, 216.89]		100.45]
$AUC_{(0-t)}$	Mean[c]	189.96	192.20	98.83	[96.60,
µg • h/mL	95% CI[d]	[175.70, 205.39]	[177.77, 207.81]		101.12]
C_{max}	Mean[c]	20.70	19.95	103.78	[98.92,
µg / mL	95% CI[d]	[19.06, 22.48]	[18.36, 21.66]		108.87]

[a] Ratio (solution/tablet) of the treatments.
[b] The 90% confidence interval for the ratio of the treatments.
[c] Geometric mean = antilogarithm of the least squares mean from the ANOVA on log transformed data
[d] The 95% confidence interval for the mean.

Table 2: Parametric Analyses for AUC, AUC(0-t) and Cmax Following a Single Oral Dose Levetiracetam Given Either as 7.5 mL (750 mg) of an Oral Solution or a 750 mg Tablet to Healthy Volunteers

Safety Summary: Both formulations were reported by the sponsor to be well tolerated. No deaths or other serious adverse events occurred during the study or within 4 weeks after the final dose of study were reported by the sponsor.

Conclusion: The results of this study support the conclusion that levetiracetam 750 mg administered as a 10% oral solution is bioequivalent to levetiracetam administered as a 750 mg tablet following single oral doses in fasting healthy subjects. Both formulations were reported by the sponsor to be well tolerated.

Reviewer's comments: *The reviewer agrees with the sponsor's conclusions.*

APPEARS THIS WAY
ON ORIGINAL

Title (N160, RRCE99H0901): Open Label, One Way, One Sequence Cross-Over Study to Assess the Effect of Valproate Steady State Administration on the Single Dose Pharmacokinetics of Levetiracetam (1500, per os, 500 mg Tablets) in Healthy Male and Female Volunteers

Objectives: 1) To provide evidence that valproate (VPA) in steady state conditions was unlikely to interact with the pharmacokinetics of ucb L059, and if likely, to estimate with reasonable precision the extent of interaction and to give recommendations on whether and how to adapt the dosing of ucb L059. The primary endpoint was the AUC of plasma concentration of levetiracetam (ucb L059).

The secondary objectives of the study were

a) To determine the possible influence of VPA in steady state conditions on the pharmacokinetic parameters of ucb L057 (metabolite of ucb L059)
b) To gain some information on the pharmacokinetic parameters VPA in the presence of ucb L059
c) To gain additional information on the clinical safety and tolerability of ucb L059 when coadministered with VPA

Study Design: This was an open-label, single dose, one-way cross over study assessing the effect of steady state VPA administration (500 mg b.i.d. per os for 8 days) on single dose pharmacokinetics of ucb L059. Sixteen healthy volunteers between the ages of 18 to 55 years were enrolled. A single dose of 1500 mg ucb L059 (3 tabs of 500 mg) was taken orally on day 1 in the morning. From day 3 to 11, VPA (500 mg b.i.d. orally) was administered to reach steady state plasma levels from day 10 onwards. A single dose of 1500 mg ucb L059 was taken again on day 10 in the morning. The batch no. of levetiracetam 500 mg tablets was 1362 and for valproate [redacted] was 98116. A multipoint pharmacokinetic profile was performed for ucb L059 and it's major metabolite ucb L057 from day 1 to 3 and from day 10 to 12. Achievement of steady state conditions of VPA was checked by trough plasma levels measurement and a multipoint pharmacokinetic steady state profile was performed for VPA on day 10.
Blood samples for analyses of ucb L059 and L057 concentrations were collected at the following time periods: 0, 20, 40 mins, 1, 1.5, 2, 3, 4, 6, 9 and 13 hours on days 1 and 10. On days 2 and 11, samples 24 and 36 hours and days 3 and 12 at 48 hours. Blood samples were collected for plasma analyses of trough levels of VPA before 2, 5, 9, 13, and 15th dose of VPA.

Analytical Method: Levetiracetam was measured in plasma samples by a validated [redacted]. Calibration curves ranging from [redacted] were used. The mean of daily adjusted recoveries of ucb L059 plasma QC samples analyzed within the study were of 105.8, 101.7 and 99.0% at the nominal concentrations of [redacted]. The assay of the metabolite (L057) was measured in plasma samples using a validated [redacted]. Calibration curves ranging from [redacted] were used. The mean daily adjusted recoveries of ucb L057 plasma QC samples analyzed within the study were 110.6, 106.7 and 106.9% at nominal concentrations of [redacted], respectively. Levetiracetam (ucb L059) was measured in urine samples by a validated [redacted]. Calibration curves ranging from [redacted] were used. The mean of daily adjusted recoveries of ucb L059 urine QC samples analyzed within the study were of 104.7, 99.9 and 101.1% at nominal concentrations of [redacted] respectively.

Data Analysis: Pharmacokinetic parameters were computed using non compartmental methods. Lack of interaction was concluded if the 90% confidence interval for the ratio of the averages of AUC for ucb L059 (Ln transformed data) with and without VPA treatment was within the range 80 to 125%.

Results: The mean pharmacokinetic profiles for levetiracetam (ucb L059) and its major metabolite, ucb L057 are provided in figures 1 and 2 (attached). The mean pharmacokinetic parameters for levetiracetam (ucb L059) and its metabolite (ucb L057) when levetiracetam is administered alone and with VPA are provided in the following tables

Table 1: Pharmacokinetic parameters of Levetiracetam (ucb L059) after administration of a 1500 mg single oral dose of Levetiracetam either alone or with valproate

Pharmacokinetic Parameter	Unit	Levetiracetam alone	Levetiracetam with VPA	Ratio of geometric* mean (90% CI)
		Mean ± SD		
Cmax	µg/mL	39.6 ± 9.9	41.4 ± 9.7	104.7 (95.9,114.4)
Tmax[a]	h	0.67 (0.33 – 2.0)	0.67 (0.33-2.0)	0.00 (-0.29,0.13)[b]
λz	1/h	0.095 ± 0.014	0.094 ± 0.012	99.2 (97.6,100.7)
AUC	µg*h/mL	400 ± 47	397 ± 60	98.9 (96.2,101.6)
CL/F	mL/min/kg	0.89 ± 0.11	0.90 ± 0.13	101.1 (98.4,103.9)
Vz/F	L/kg	0.57 ± 0.07	0.58 ± 0.08	101.8 (99.4,104.3)
Ae	mg	939 ± 85	871 ± 113	92.9 (89.1,97.0)
fe	%	62.6	58.1 ± 7.6	

[a]Cmax, peak plasma concentration; tmax, time to reach Cmax; AUC, area under the plasma concentration-time curve extrapolated at infinite time; λz, terminal rate constant; Cl/f, apparent plasma clearance; Vz/f, volume of distribution; Ae and fe, cumulative amount excreted in urine over 48 hours in mg and % of the dose, respectively. [a]Median (min-max). [b]Median difference between test and reference and 90% CI of difference. *Computed from back transformation of the difference of least square means between test (co-administration with VPA and reference (levetiracetam alone) treatment

Table 2: Pharmacokinetic parameters of ucb L057 after administration of a 1500 mg single oral dose of Levetiracetam either alone or with valproate

Pharmacokinetic Parameter	Unit	Levetiracetam alone	Levetiracetam with VPA	Ratio of geometric mean (90% CI)
		Mean ± SD		
Cmax	µg-eq/mL	1.08 ±0.20	1.02 ± 0.22	94.1 (89.8,98.6)
Tmax[a]	H	6 (3 – 9)	6 (3- 9)	1.00 (0.00,1.50)
λz	1/h	0.082 ± 0.011	0.082± 0.011	100 (97.4,102.8)
AUC	µg-eq*h/mL	23 ± 6.5	21.9 ± 6.3	95.0 (90.3,99.9)
CL/F	ML/min/kg	0.89 ± 0.11	0.90 ± 0.13	101.1 (98.4,103.9)
Ae	Mg-eq	308 ± 75	275 ± 58	87.9 (84.7,91.3)
fe	%	20.5 ± 5.0	18.3 ± 3.9	-

[a]Cmax, peak plasma concentration; tmax, time to reach Cmax; AUC, area under the plasma concentration-time curve extrapolated at infinite time; λz, terminal rate constant; Cl/f, apparent plasma clearance; Ae and fe, cumulative amount excreted in urine over 48 hours in mg and % of the dose, respectively. [a]Median (min-max). [b]Median difference between test and reference and 90% CI of difference. *Computed from back transformation of the difference of least square means between test (co-administration with VPA and reference (levetiracetam alone) treatment

When levetiracetam was given alone, the peak concentration was achieved at 0.67 hours. Concentrations then declined monophasically with a half-life of 7.5 ± 1.1 hours. The 48-hour cumulative urinary excretion was 939 ± 85 mg. This is equivalent to 62.6 ± 5.7% of the given dose. The renal clearance of ucb L059 was 0.58 ± 0.09 ml/min/kg. Multiple-dose co-administration of VPA 500 mg bid did not significantly alter the pharmacokinetics of levetiracetam. The 90% CI was within 80 to 125.

Multiple-dose co-administration of VPA 500 mg b.i.d did not modify the extent and rate of exposure to levetiracetam. The cumulative urinary excretion of levetiracetam and its pharmacokinetic behavior were also not significantly altered when compared to the parameter values obtained for levetiracetam, when levetiracetam was given alone.

Table 3: The mean trough concentrations and pharmacokinetic parameters for VPA are provided in the following table.

PK Parameter	Unit	Study Day							
		Day 3	Day 4	Day 5	Day 7	Day 9	Day 10	Day 11	Day 12
AM trough	µg/mL	-	56.7 ± 19.9	53.8± 17.6	60.1 ± 17.0	75.6 ± 25.0	84.5 ± 21.2	78.7 ± 26.0	74.6 ± 26.4
PM trough	µg/mL	32.1 ± 11.5	-	-	-	-	65.7 ± 20.0	72.5 ± 25.2	-
Cmax	µg/mL	-	-	-	-	-	93.7 ± 19.9	-	-
tmax	H	-	-	-	-	-	2.90 ± 3.62	-	-
AUC (0-12h)	µg*h/ mL	-	-	-	-	-	870 ± 199	-	-
Cav	µg/mL	-	-	-	-	-	72.5 ± 16.6	-	-
PTF AM	-	-	-	-	-	-	0.12 ± 0.15	-	-
PTF PM	-	-	-	-	-	-	0.40 ± 0.22	-	-

PTF, peak to trough concentration.

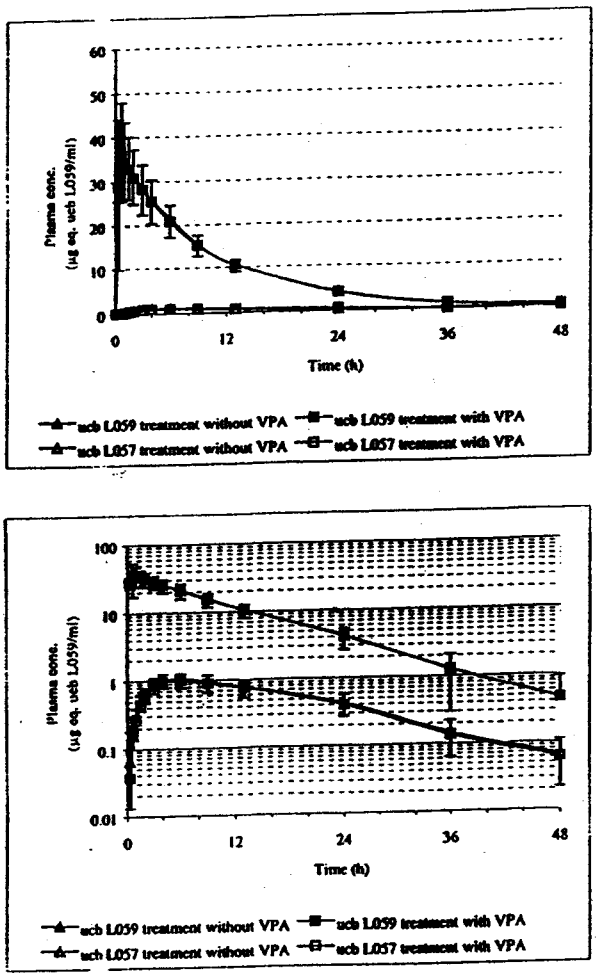
Trough plasma concentrations on days 9 to 12 suggest that steady state was reached by day 10 following seven days of twice daily administration of 500 mg Depakine enteric.

Safety Summary: The sponsor reported that no serious adverse events were reported. The most frequently reported adverse event reported during either treatment were dizziness, asthenia, nausea, headache and dry mouth.

Summary: Multiple dose co-administration of VPA b.i.d. did not significantly modify the extent and rate of exposure of levetiracetam. The sponsor stated that no dose adjustment of levetiracetam is needed when levetiracetam is co-administered with valproate. Steady state trough concentrations were obtained within 10 days of VPA multiple dose administration of VPA. The sponsor reports that trough concentrations and pharmacokinetic parameters of VPA are consistent with reported interaction studies conducted in healthy volunteers, using similar dosing regimen. Hence, the sponsors states that levetiracetam does not significantly affect the pharmacokinetics of VPA.

Reviewer's comments: *This reviewer agrees with the sponsor that co-administration of levetiracetam with valproate does not affect the pharmacokinetic of levetiracetam. It is not clear from this study whether valproate pharmacokinetics is altered when co-administered with levetiracetam.*

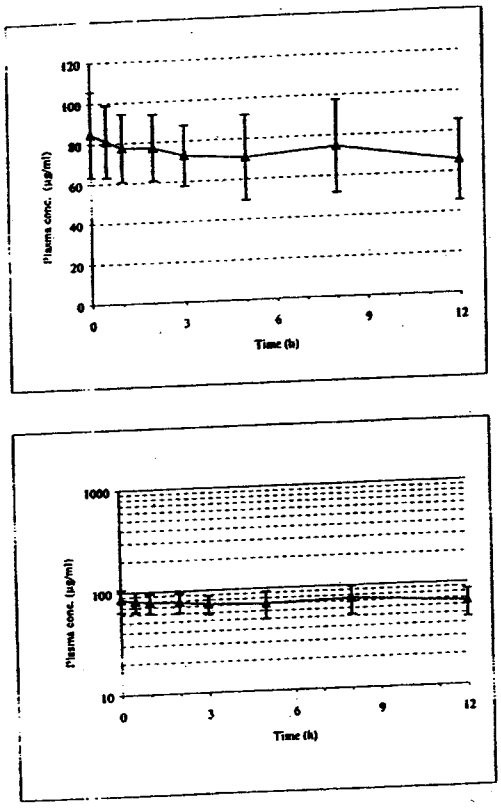
Detailed plasma data



Plasma concentrations-time profile of ucb L059 and ucb L057 in male and female healthy volunteers following a single oral administration of ucb L059 at a target dose of 1500 mg either alone or in co-treatment with valproic acid.
Data are presented as mean±SD (n=16), in lin-lin (top) and log-lin (bottom) scale.

Fig 1

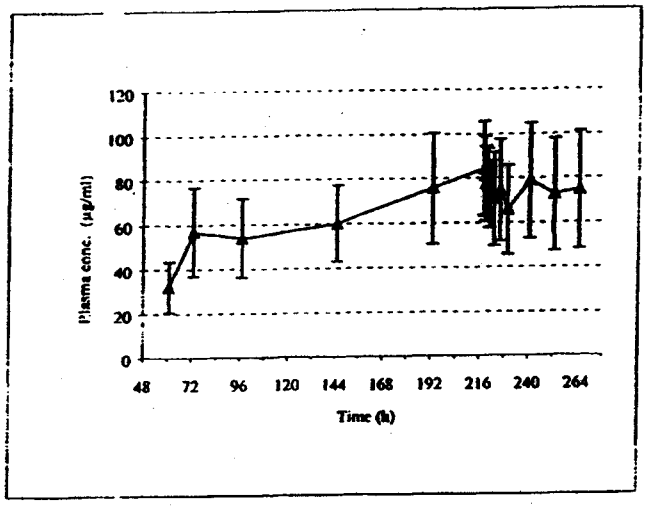
Detailed plasma data

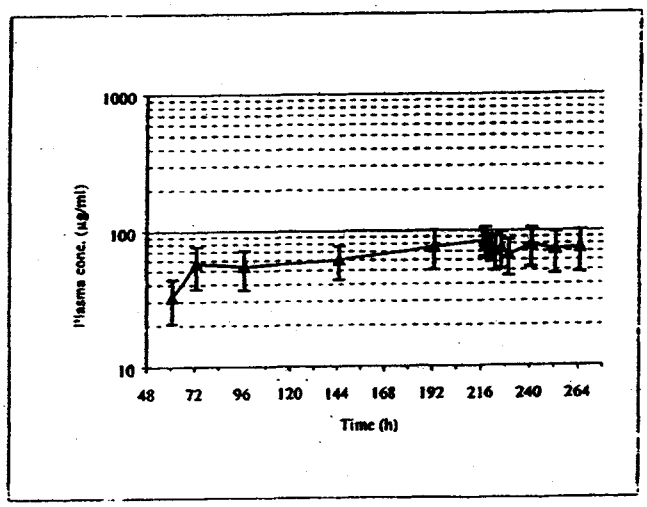


Plasma concentrations-time profile of VPA in male and female healthy volunteers following multiple oral administration of VPA at a daily target dose of 1000 mg (500 mg b.i.d. 12h apart, Day 10).
Data are presented as mean±SD (n=16), in lin-lin (top) and log-lin (bottom) scale.

Fig 2

Detailed plasma data





Plasma concentrations-time profile of VPA in male and female healthy volunteers following multiple oral administration of VPA at a daily target dose of 1000 mg (500 mg b.i.d. 12h apart). The time is expressed as the time following the first administration of ucb L059. VPA treatment was started 49 hours after the first administration of ucb L059. Data are presented as mean±SD (n=10 to 16), in lin-lin (top) and log-lin (bottom) scale.

Fig 3

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Kofi Kumi
4/2/03 10:47:45 AM
BIOPHARMACEUTICS

Raman Baweja
4/2/03 11:10:51 AM
BIOPHARMACEUTICS