

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-035	Submission Dates: 2/1/99, 4/26/99, 5/13/99
Generic Name:	Levetiracetam	
Brand Name:	Kepra	
Strengths:	250 mg, 500 mg and 750 mg Tablets	
Formulation:	IR Tablets for Oral Administration	
Indication of Drug:	Adjunctive Therapy for Partial Onset Seizures	
Sponsor:	UCB Pharma, Inc., Smyrna, Georgia	
Type of Submission:	NDA (NME)	
Reviewer:	Hong Zhao, Ph.D	

SYNOPSIS (*Question-Based*)

What is the active moiety?

Levetiracetam (ucb L059) is a single enantiomer with chemical name of (S)- α -ethyl-2-oxo-1-pyrrolidine acetamide and it is chemically unrelated to existing antiepileptic drugs.

What is the clinical indication?

For adult epileptic patients, as adjunctive therapy in refractory partial onset seizures with and without secondary generalization.

What are the dosage form, strengths and regimen?

Available as 250, 500 and 750 mg IR tablets; 1000 to 3000 mg/day given as b.i.d.

Whether pediatric will be marketed at the same time?

No. It is in the sponsor's future plan.

What class does levetiracetam belong to?

In the Biopharmaceutics Classification System, it belongs to Class I since it is highly soluble (1.04 g/ml), highly permeable (F >90%) and >85% of the tablet amount released in 15 minutes in three different pH media. Clinically, it does not belong to narrow therapeutic class because it has a relatively low order of toxicity and a relatively high therapeutic index.

How was the first dose in humans derived?

It was derived empirically. In rats and mice the acute oral toxicity (LD₅₀) is >5 g/kg. In dogs, doses >600 mg/kg cause vomiting. Sub-chronic oral toxicity studies as once daily doses for 3 months in the rat (up to 1800 mg/kg/day) and in the dog (up to 1200 mg/kg/day), showed levetiracetam to be relatively non-toxic. The preclinical

pharmacodynamic, pharmacokinetic and toxicity evaluations support the use of levetiracetam in epileptic patients at the recommended doses of 1 to 3 g/day.

What are the basic pharmacokinetic characteristics of levetiracetam?

Absorption is rapid (T_{max} at 1h in fasted subjects) and oral bioavailability is 100%. Food decreases C_{max} by 20% and prolongs T_{max} by 1.5 hours. PK is linear over the dose range of 500 to 5000 mg. Steady state is achieved after 2 days of twice daily dosing and there is no unexpected accumulation. Plasma elimination half-life in adults is 7 ± 1 hours and is unaffected by either dose or repeated administration. It is $<10\%$ bound to plasma protein. The volume of distribution (V_d) is 0.6 L/kg. It is eliminated from systemic circulation by renal excretion as unchanged drug (66% of dose). The total body clearance is 0.9 ml/min/kg and the renal clearance is 0.6 ml/min/kg. Its elimination is correlated with creatinine clearance. There is no age, gender, race or circadian effect.

How variable is the drug?

Overall the variability is less than 30%.

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What are the metabolic pathways?

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is an enzymatic hydrolysis of the acetamide group producing the carboxylic acid metabolite, ucb L057 (24% of dose). This metabolite is renally excreted with renal clearance of 4 ml/min/kg. The hydrolysis is mediated by amidases probably located in the cytosol and reported as non-inducible. Other identified metabolites are less than 2% each. Levetiracetam metabolism is not dependent on any liver cytochrome P450 isoenzymes.

Is the major metabolite active?

No. The major metabolite (24% of dose) is inactive and is not associated with any safety concerns in non-clinical studies.

Is there any in vivo enantiomeric interconversion?

No. There is no enantiomeric interconversion of levetiracetam or its major metabolite.

Should we expect any metabolic or protein binding drug-drug interaction?

No. Metabolism of levetiracetam is independent of liver cytochrome P450 isoenzymes. The plasma protein binding of levetiracetam and ucb L057 is less than 10%.

What is the most important in vivo drug-drug interaction that we should be concerned with?

The main clinical concern would be does levetiracetam increase the levels of existing AEDs such as carbamazepine, phenytoin, valproic acid, lamotrigine, gabapentin, phenobarbital and primidone. Levetiracetam neither increases nor decreases the steady-state serum concentrations of these AEDs. In turn, these AEDs also do not affect the pharmacokinetics of levetiracetam.

Is there any other clinically important drug-drug interaction?

No. Levetiracetam does not change the pharmacokinetics of warfarin, digoxin or oral contraceptives (ethinylestradiol and levonorgestrel). These drugs do not affect the pharmacokinetics of levetiracetam.

What would be the impact of a renal tubular secretion-blocking drug (e.g., probenecid) on levetiracetam disposition?

The rate and extent of exposure of levetiracetam and its renal clearance were not affected. In the presence of probenecid, the C_{max} of ucb L057 was 2.2-fold and its renal clearance was 40% of that without probenecid. No dose adjustment is necessary.

Is there any dosage adjustment necessary for levetiracetam in special populations?

Except for renally impaired patients and patients undergoing hemodialysis, there is no dosage adjustment necessary for hepatically impaired patients, elderly, gender or race.

What special dosing recommendations are being provided for the renally impaired patients and patients undergoing hemodialysis?

Renal impairment studies show that levetiracetam clearance decreased by 40% in mild, and by 60% in both moderately and severely renally impaired patients. Total body clearance and renal clearances of the levetiracetam were well correlated to creatinine clearance. Adjustment of the daily maintenance dose is proposed for patients as follows:

Group Renal Function	Creatinine Clearance (ml/min)	Dosage (mg)	Frequency
Normal	>80	500 to 1,500	Every 12 h
Mild			
Moderate	30-50	250 to 750	Every 12 h
Severe			

In anuric ESRD patients, total body clearance was only 30% of that in healthy subjects; half-life on inter-dialysis periods averaged 25 hours as compared to 3.1 hours during intra-dialysis periods; approximately 50% of the dose was removed during a typical 4-hour dialysis session.

It is recommended that naive ESRD patients maintained on hemodialysis receive 500 to 1000 mg dose every 24 hours. Following dialysis, a 250 to 500 mg supplemental dose should be given as the dialysis unit removes 50% of the dose.

Is the to be marketed tablet (TBM) the same as the clinically studied tablet?

The TBM tablet (500 mg yellow) differs from the clinically studied tablet (500 mg white) in color only. Link between these two formulations is made through dissolution.

How are the 250 mg and 750 mg tablets linked to the 500 mg tablets?

Based on linear kinetics of the drug, compositional proportionality amongst the three tablet strengths and similar dissolution profiles.

Are the analytical methods validated?

Yes. The analytical methods have been validated for linearity, precision, accuracy, recovery, sensitivity and stability. They are acceptable.

Does the dose correlate with the clinical efficacy end point?

The clinical efficacy end point is percent reduction in weekly seizure frequency (SF). There is a greater median percent reduction in Type I seizure frequency with increasing dose. Also, the proportion of responders ($\geq 50\%$ reduction from baseline in weekly seizure frequency) is higher with increasing dose. The response rates are as following:

Dose (N)	Placebo (N=301)	1000mg (N=195)	2000mg (N=95)	3000mg (N=269)
Response Rate	12.6%	27.7%	31.6%	41.3%

Did the sponsor attempt any PK/PD relationship for the drug?

No, although they were advised to do so at the end of Phase II meeting.

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RECOMMENDATION

This submission (NDA 21,035) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) and has been found to be acceptable for meeting the OCPB requirements. The sponsor is requested to adopt the OCPB labeling as provided in this review. Also, the sponsor is requested to adopt the dissolution methodology and specification for all three strengths of levetiracetam tablets, as outlined in Comment #1 to the sponsor.

COMMENTS TO CLINICAL DIVISION

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Comment 1

Renal impairment studies show that levetiracetam clearance decreased by 40% in mild, and by 60% in both moderately and severely renally impaired patients. Total body clearance and renal clearances of the levetiracetam were well correlated to CL_{Cr}. Adjustment of the daily maintenance dose is proposed for patients as follows:

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It is recommended that naive ESRD patients maintained on hemodialysis receive 500 to 1000 mg dose **every 24 hours**. Following dialysis, a 250 to 500 mg supplemental dose should be administered because the dialysis unit removes 50% of levetiracetam dose.

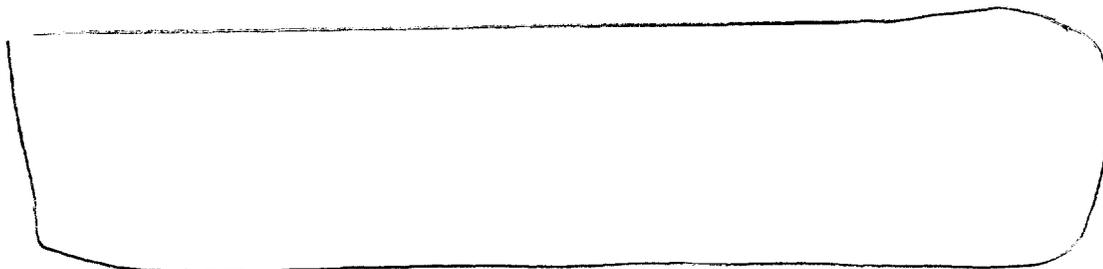
Comment 2

Pharmacokinetically, levetiracetam neither increases nor decreases the steady-state serum concentrations of carbamazepine, phenytoin, valproic acid, lamotrigine, gabapentin, phenobarbital and primidone in patients receiving constant doses of these AEDs. This indicates that levetiracetam exerts its clinical outcome pharmacologically rather than affecting plasma concentrations of the existing antiepileptic drugs.

COMMENTS TO THE SPONSOR

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Comment 1



Comment 2

The sponsor is encouraged to attempt PK/PD correlation in the course of their drug development programs.

INTRODUCTION

Levetiracetam (ucb L059) is a new molecular entity and is the active ingredient of Kepra tablets. The chemical name for this single enantiomer, is (S)- α -ethyl-2-oxo-1-pyrrolidine acetamide and it is chemically unrelated to existing antiepileptic drugs (AEDs). The drug is highly soluble and highly permeable. The intended clinical indication is for adult epileptic patients, as adjunctive therapy in refractory partial onset seizures with and without secondary generalization. The recommended dose range in humans is 1000 to 3000 mg/day in a b.i.d. regimen.

Levetiracetam (5-50 mg/kg p.o.) demonstrates potent, broad spectrum protection in animal models of partial and primary generalized seizures. It appears to lack any notable cardiovascular and respiratory effects and has no mutagenic, clastogenic or carcinogenic potential based on animal studies. In rats and mice the acute oral toxicity (LD_{50}) of levetiracetam is greater than 5 g/kg. In dogs, doses exceeding 600 mg/kg cause vomiting. Sub-chronic oral toxicity studies in the rat, at dose up to 1800 mg/kg/day and in the dog, at doses up to 1200 mg/kg/day, showed levetiracetam to be relatively non-toxic when administered as once daily oral doses for 3 months. The preclinical pharmacodynamic, pharmacokinetic and toxicity evaluations support the use of levetiracetam in epileptic patients at the recommended doses of 1 to 3 g/day.

In humans, 66% of an oral dose of levetiracetam is excreted unchanged in urine. The major metabolite (ucb L057), accounting for approximately 24% of the dose, is obtained by hydrolysis of the acetamide to a carboxylic acid. The reaction has been shown to occur in a large variety of tissues and in whole blood but not in plasma and is mediated by an amidase, probably located in the cytosol and reported as non-inducible. The role of the liver in the metabolism of levetiracetam is limited, as the non-renal clearance is only reduced by 36% in severe hepatic impaired subjects. Other metabolites represent less than 2% of the dose each. The metabolite ucb L057 is devoid of relevant anticonvulsant activity in animals.

Levetiracetam appeared to be generally well tolerated when administered as single oral doses of 500 to 5000 mg or as multiple doses of 1500 mg b.i.d. for 7 days to healthy volunteers. In long term studies, doses up to 4000 mg/day were used and were well tolerated. The most frequently reported adverse events associated with the use of levetiracetam in combination with other AEDs, were somnolence, asthenia, infection and dizziness, which were not seen at an equivalent frequency among placebo-treated patients.

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SUMMARY OF PHARMACOKINETIC STUDIES Levetiracetam (ucb L059)

Pharmacokinetics in Healthy Volunteers

What type of PK studies have been conducted?

Five formal single dose and two multiple dose levetiracetam pharmacokinetic studies have been conducted in healthy volunteers. Metabolism and mass balance of levetiracetam were studied in a radiolabeled study. Evaluating dose proportionality following doses of up to 5000 mg was conducted in white male volunteers and in male Japanese volunteers.

Absolute and relative bioavailability of levetiracetam capsules versus an intravenous solution and an oral solution was evaluated in a single dose study. The bioequivalence (BE) of capsules and tablets used in clinical trials was demonstrated in a BE study. The pharmacokinetics and urinary excretion of levetiracetam and its metabolite, ucb L057 were characterized in male Japanese volunteers.

Mass-Balance

What are the basic PK characteristics?

In Study N046 (U.K.), 4 healthy male subjects were administered single 500 mg oral dose of ¹⁴C-ucb L059. The levels of total radioactivity and ucb L059 in plasma after dosing is shown in the attached figure (P.7a). The major pharmacokinetic parameters are listed below:

Parameter	C _{max} (µg/ml)	AUC (µg.h/ml)	t _{1/2β} (h)	V _{d/f} (L/kg)	CL/f (ml/min/kg)	T _{max} (h)
N=4						
Mean±SD	15.0±1.9	117±24	7.6±0.3	0.60±0.03	0.96±0.15	0.4±0.1

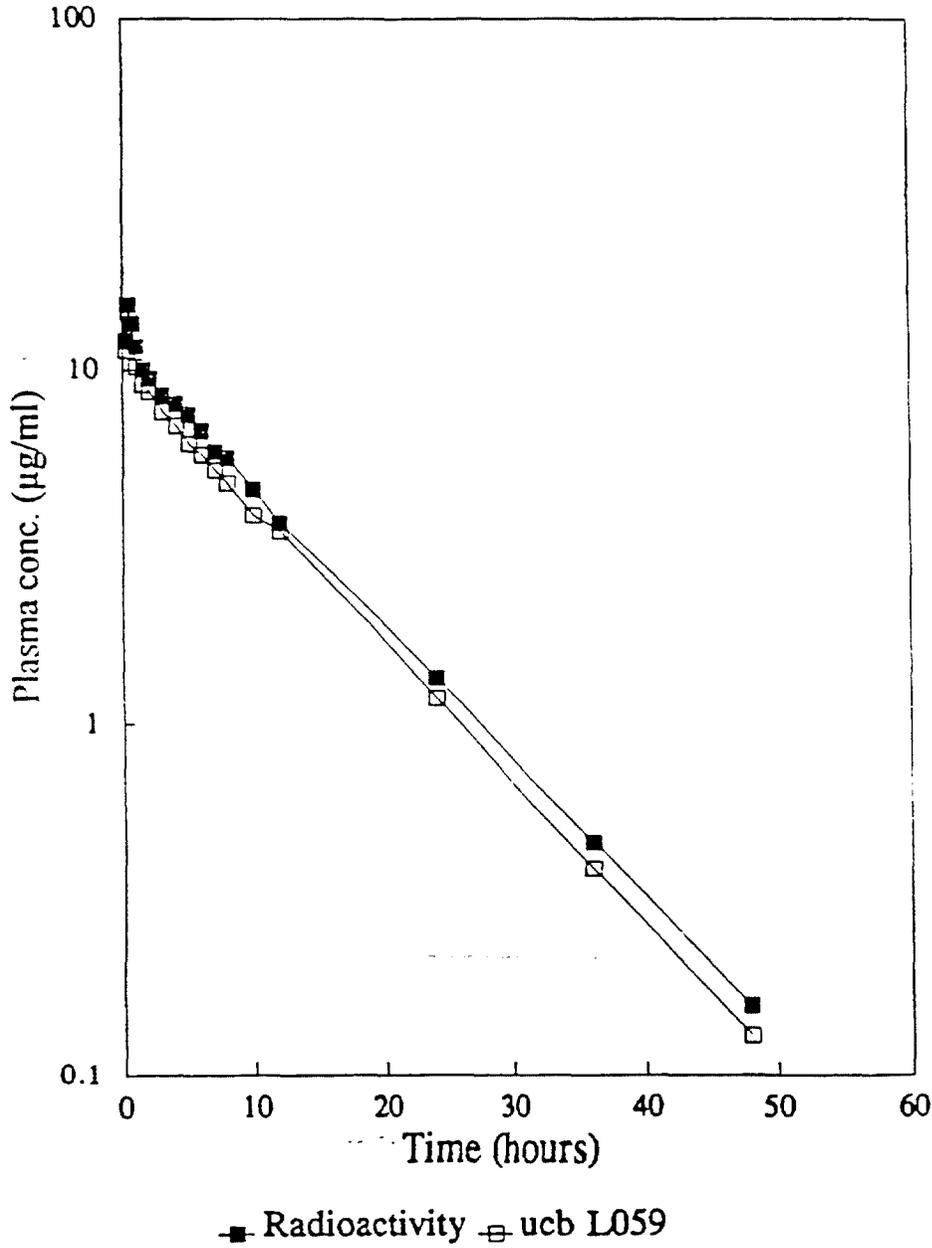
The apparent volume of distribution (V_{d/f}) of 0.60 L/kg is close to the volume of intracellular and extra-cellular water. The terminal half-life (t_{1/2β}) is in close agreement with excretion half-life measured in urine (7.9 hours). The mean apparent total body clearance (CL/f) of 0.96 ml/min/kg is much lower than the normal hepatic blood flow (21 ml/min/kg), suggesting that extensive first pass metabolism does not occur. Protein binding studies indicated that ¹⁴C-ucb L059 did not bind to plasma proteins to any significant extent (<10%). The plasma to blood ratio was 1.25.

How is the drug eliminated?

The major route of excretion was via urine, accounting for a mean of 95% of the administered radioactivity with approximately 93% excreted within 48 hours, and 0.3% via feces. From 48-hour urine samples, the following components were recovered:

Compound	ucb L059	ucb L057	ucb R297	ucb K115	Others
% Dose	65.9±1.2	23.7±1.9	1.6±1.5	0.9±0.6	0.6±0.6

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Figure 2.

Mean Levels of Total Radioactivity and of ucb L059 in Plasma Following Single Oral Administration of [¹⁴C]-ucb L059 to Four Male Human Volunteers at a Target Dose of 500 mg per Volunteer.

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Levetiracetam is excreted by glomerular filtration with subsequent partial tubular reabsorption with a renal clearance of 0.6 ml/min/kg. The major metabolite ucb L057 (24% of dose) is excreted by glomerular filtration and active tubular secretion with a renal clearance of approximately 4 ml/min/kg and elimination half-life of 10 hours.

What are the metabolic pathways?
Is the major metabolite active?

Levetiracetam is not extensively metabolized in humans. The metabolic pathways detected in human volunteers are identical to that in animal species and are depicted in the attached figure (P. 8a). The major metabolic pathway is an enzymatic hydrolysis of the acetamide group producing a pharmacologically inactive carboxylic acid metabolite, ucb L057. The hydrolysis is mediated by amidases probably located in the cytosol and reported as non-inducible. Other identified metabolites are less than 2% each. Levetiracetam metabolism is not dependent on any liver cytochrome P450 isoenzymes.

Is there any in vivo enantiomeric interconversion?

No enantiomeric interconversion of levetiracetam and the major metabolite occurred *in vivo* in the human volunteers enrolled in the study as determined by chiral HPLC. There were no detectable ucb L060 and ucb L058 (corresponding R-enantiomers). In addition, there were no differences in plasma levels among the different compounds (ucb L059, racemic mix-ucb 6474 and R-enantiomer-ucb L060) at equivalent doses (up to 5000 mg as single oral doses) administered to student volunteers in Studies N001 and N002.

Pharmacokinetics after Single dose and Multiple Doses

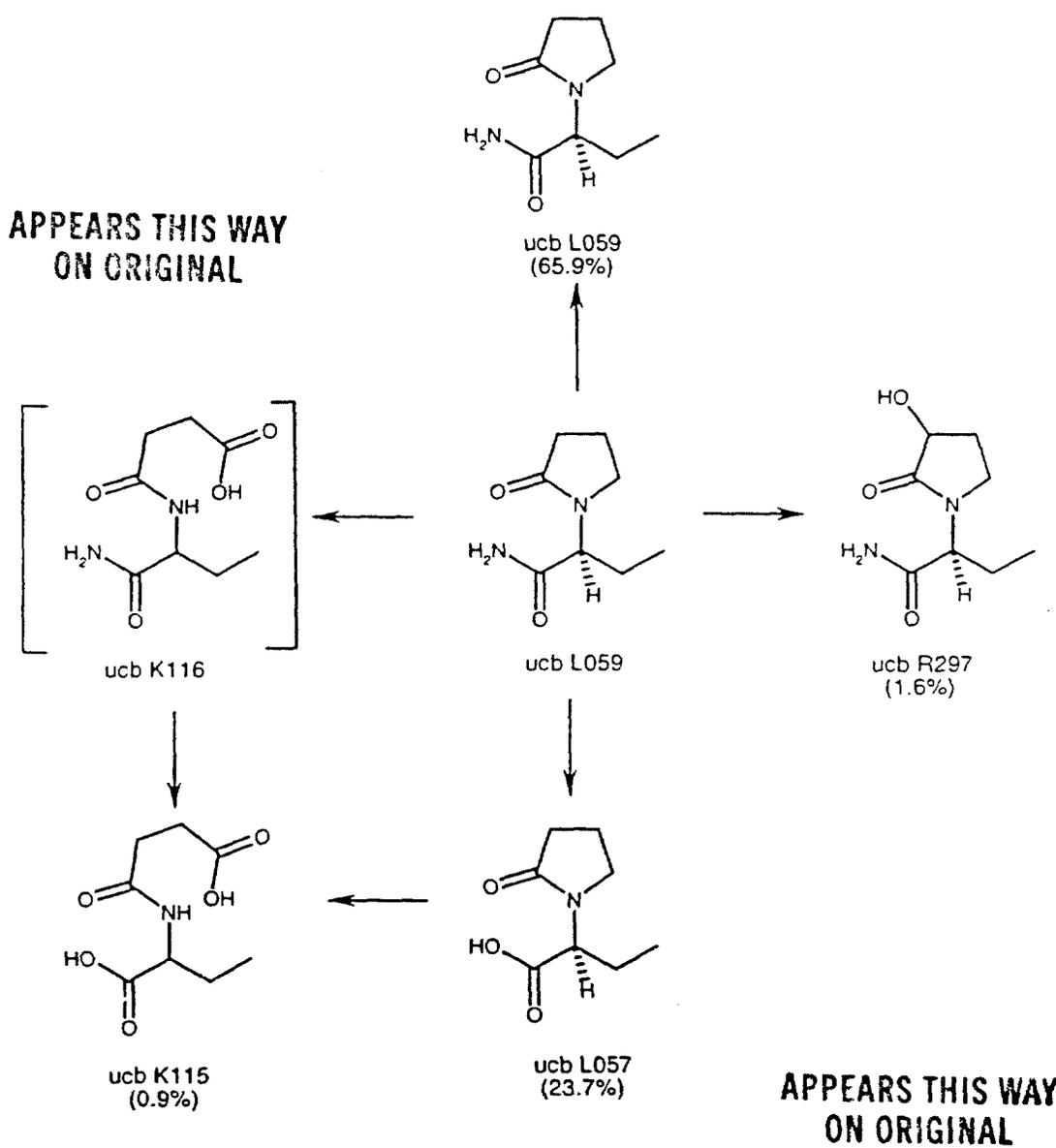
Is multiple dose PK predictive from single dose PK?
Do the parent drug and metabolites accumulate?

Five formal single dose pharmacokinetic studies (N205, N069, N046, D002 and N201) and two multiple dose studies (N128 and N202) have been conducted in healthy volunteers. The results show that levetiracetam is rapidly and almost completely absorbed in man after oral administration. Absorption half-life is 0.2 hours on average and peak levels were generally reached within 1 hr after administration. Oral bioavailability is close to 100%. The major pharmacokinetic parameters of levetiracetam are listed below:

Parameter	T_{max} (h)	$t_{1/2}$ (h)	Vd (L/kg)	CL/f (ml/min/kg)
Mean±SD	1.3±0.7	7.2±1.1	0.60±0.03	0.96±0.14

Steady state was reached after 2 days of dosing. There was no evidence of unexpected accumulation as evidenced by the mean ratio of 1.6 for AUC_{0-12h} at steady state to AUC_{0-12h} after single dose; the theoretical value (R) is 1.4. Elimination half-life does not vary with dose, the route of administration, or after multiple dosing. There were no noteworthy changes in pharmacokinetics, including urinary excretion, after repeated dosing.

Figure 9
Human Metabolic Pathways



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Dose Proportionality

Is PK of levetiracetam linear?

Dose proportionality was evaluated in European and Japanese subjects (D002 and N201). In Study D002 (Ireland), levetiracetam was given to 6 young male subjects over the dose range of 500 mg to 5000 mg. Subjects received doses on Day 1 (500 mg), Day 4 (1000 mg), Day 7 (2000 mg), Day 10 (3500 mg), and Day 13 (5000 mg). See attachment for plasma concentration-time profiles, and C_{max} vs. dose and AUC vs. dose plots (P.9a). The ratios are listed below:

Dose (mg)	500	1000	2000	3500	5000
Dose ratio	1.0	2.0	4.0	7.0	10.0
C_{max} ratio	1.0	2.7	4.7	9.2	11.6
AUC ratio	1.0	1.9	4.0	6.4	9.2

After oral administration of levetiracetam, peak plasma levels and AUCs are proportional indicating linearity of exposure up to 5000 mg. Similar dose proportionality up to 5000 mg of levetiracetam was observed in Japanese subjects.

Absolute and Relative Bioavailability

What is the absolute and relative bioavailability of the drug?

Study N069 (Belgium) was conducted to evaluate the bioavailability of two oral formulations of levetiracetam (solution and capsules) relative to intravenous administration at dose of 1000 mg. Twelve young male subjects were enrolled in this three-period, single dose, crossover study with a 7-day washout between periods. The extent of bioavailability was assessed by comparison of $AUC_{0-\infty}$ as follows:

$AUC_{0-\infty}$	Solution/i.v.	Capsule/i.v.	Capsule/Solution
Ratio	1.06±0.11	1.01±0.12	0.96±0.06

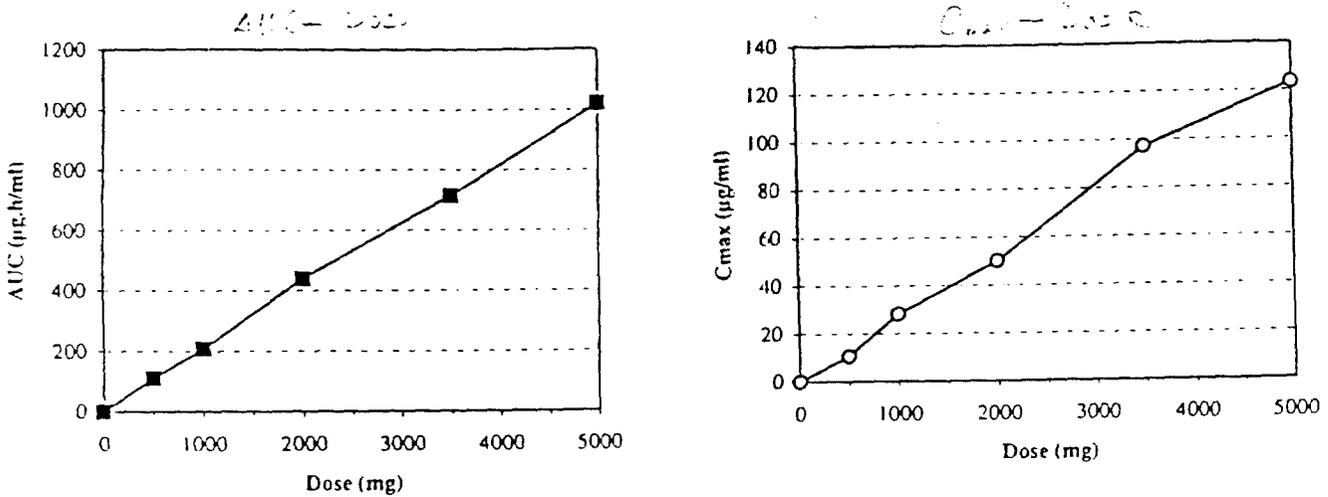
The data indicate that the extent of bioavailability of the three formulations is equivalent.

Tablet and Capsule Bioequivalence

Are the capsules and tablets used in clinical studies bioequivalent?

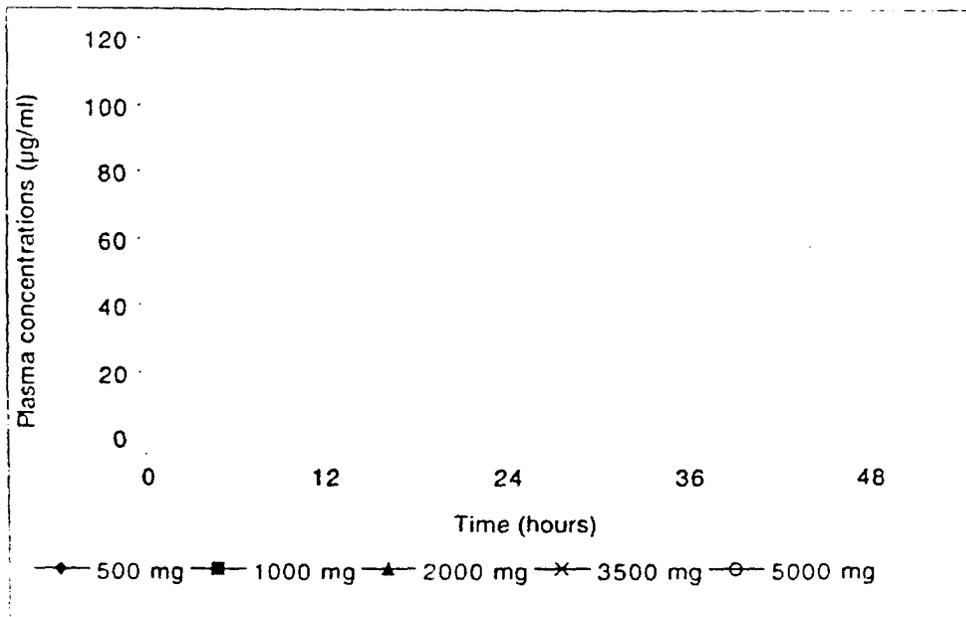
Study N128 (Germany) was to evaluate the bioequivalence of two formulations of levetiracetam, a 500 mg tablet (Batch No.84, comparable to the proposed commercial formulation and used in pivotal clinical trials) and 2x250 mg capsule (Batch No.31, comparable to lots used in several clinical trials), in 24 healthy volunteers (13 males and 11 females). A single dose of 500 mg was administered in a crossover fashion. The mean ratios of the tablet to the capsule for C_{max} and $AUC_{0-\infty}$ and 90% confidence intervals (CI) are shown below indicating that these tablets and capsules are bioequivalent.

Figure 7
Mean Area under the Plasma Concentration Time Curve following Single Oral Doses of Levetiracetam in Healthy Volunteers (500 to 5000 mg)



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Figure 8
Time Course of Plasma Levels of Levetiracetam in Healthy Volunteers after a Single Oral Dose (500 mg to 5000 mg)



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D. 9a

	Ratio	90% CI
AUC _{0-∞}	105.6%	99-109%
C _{max}	103%	94-115%

Food Effect

Does food affect the rate and extent of levetiracetam absorption?

In Study N206 (United States), 19 young male volunteers received single dose of 1000 mg (2x500 mg tablets) levetiracetam with a 5- to 8-day washout between periods. For subjects in fed condition, a breakfast (one fried egg, one buttered English muffin, one slice of Canadian bacon, one slice of American cheese, one serving of hash brown potatoes, 8-oz of whole milk, and 6-oz of orange juice) was given 0.5 hours prior to dosing. Major pharmacokinetic parameters of levetiracetam are listed below:

Parameter N=19	C _{max} (µg/ml)	T _{max} (h)	AUC _{0-∞} (µg.h/ml)	T _{1/2} (h)
Fasted	20.1±3.3	0.7±0.3	223±28	8.3±1.1
Fed	16.6±2.1	2.3±1.3	200±19	8.0±0.7
Fed/Fasted				
90% CI	79%- 88%		87%- 93%	

Coefficient of variation for all parameters was less than 20% except for T_{max}, which was 35% for fasting condition and 56% for fed condition.

In Study N203 (Japan), 12 young Japanese male volunteers were randomized to receive a single 1500 mg dose (3x500 mg tablets) after fasting or in the fed condition in a crossover fashion with a 2-week washout period between the two conditions. The breakfast contained 70 g protein, 60 g fat, 295 g carbohydrates and 10-11 g salt for a total of 2000 kcal. See attachment (P.10a) for the concentration-time plot. The major pharmacokinetic parameters of levetiracetam are shown below:

Parameter N=12	C _{max} (µg/ml)	AUC _{0-∞} (µg.hr/ml)	T _{max} (hr)	T _{1/2} (hr)
Fasted	50±13	470±59	0.8±0.4	7.6±0.9
Fed	36±5	437±44	2.1±1.0	7.6±0.8
Fed/Fasted	74.4	93.2		
90% CI	69-80	91-96		

Overall, food decreased C_{max} by 20% and increased T_{max} by 1.5 hr. AUC_{0-∞} decreased less in magnitude (<10%). T_{1/2} was similar between fasted and fed conditions. In conclusion, the intake of food would not have much influence on the extent of levetiracetam absorption but the rate of absorption significantly decreased.

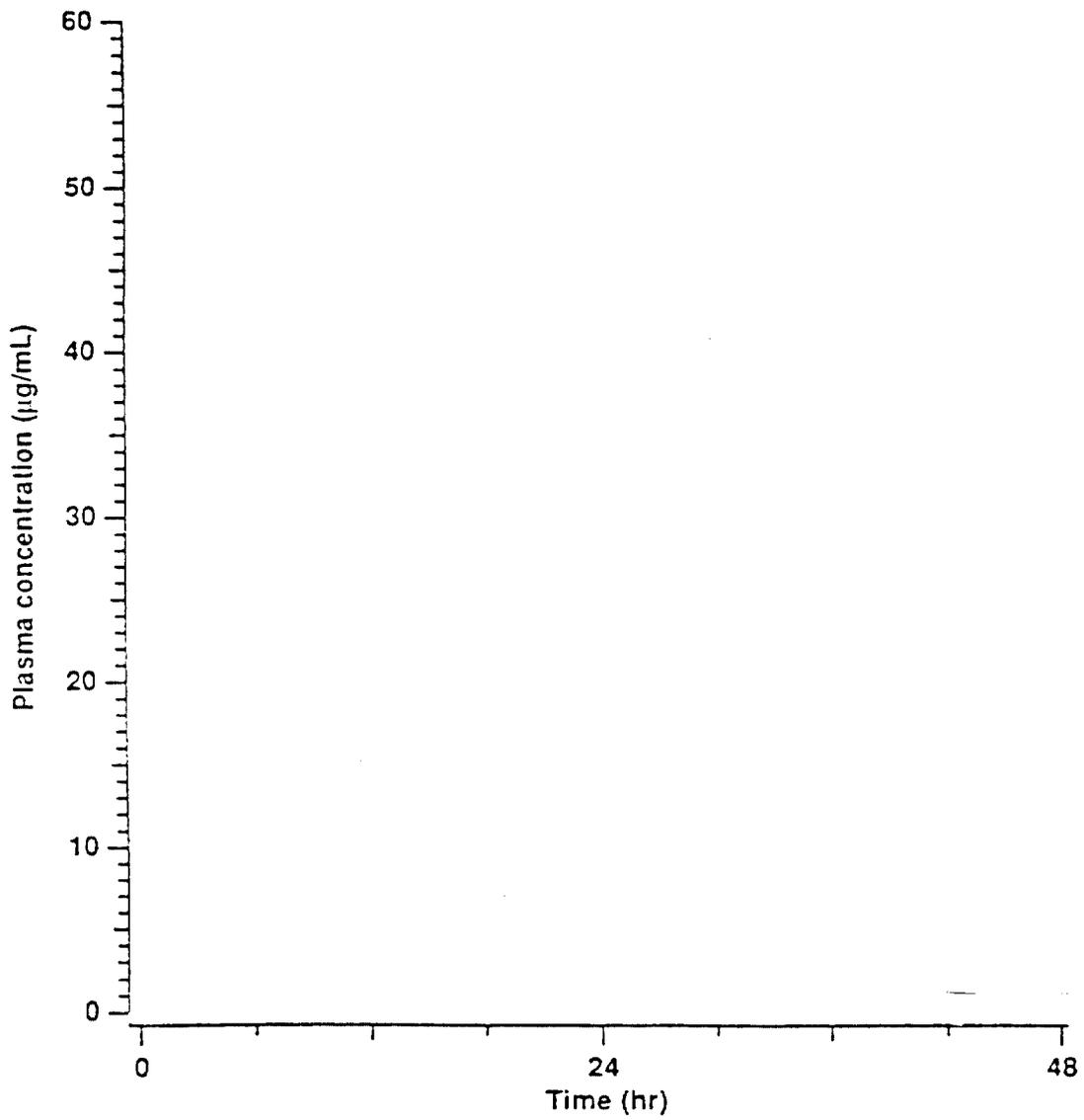


Fig. 1: Plasma concentrations of L059 and its metabolite L057 after single administration of L059 under fasted and non-fasted conditions

Dose: 1500 mg
 Each point represents the mean \pm S.D. (n=12)
 Fasted group: Δ -; ucb L059, \circ -; ucb L057
 Non-fasted group: \blacktriangle -; ucb L059, \bullet -; ucb L057

Effects of Age, Race, Gender and Circadian Rhythm on Levetiracetam Pharmacokinetics

Age Effect

Effect of age on the pharmacokinetic disposition of levetiracetam was evaluated in 214 healthy adult subjects and the results (listed below) show that the disposition of levetiracetam was comparable in subjects of 18 to 39 years and 40 to 60 years.

Parameter <i>Age (Years)</i>	T _{max} (h)	t _{1/2} (h)	CL/f (ml/min/kg)
18-39 (N=192)	1.3±0.7	7.2±1.1	0.97±0.14
40-60 (N=22)	0.9±0.4	7.3±1.2	0.92±0.11

Racial Differences

No formal pharmacokinetic studies have been conducted to determine the racial differences in the disposition of levetiracetam. In Study N128, 12 Caucasians received 500 mg levetiracetam tablets b.i.d. and in Study N202, 12 Japanese received 1000 mg or 1500 mg tablets b.i.d. (N=6 in each dosing regimen). Major pharmacokinetic data available across these two studies in healthy volunteers are shown in the table. These data indicate that there are no apparent differences between the racial groups in the pharmacokinetic disposition of levetiracetam.

Parameter <i>Race</i>	C _{max} (ng/ml)	AUC _{0-12h} (ng.h/ml)	CL/f (ml/min/kg)	t _{1/2} (h)
Caucasians (N=12)	0.61	4.1	0.91	7.5
Asians (N=12)	0.56	4.8	0.85	8.0

C_{max} and AUC values are normalized to a 1 mg/kg dose.

Gender Effects

Pharmacokinetic results of levetiracetam (1000 mg b.i.d.) from 23 healthy adult volunteers (Study N150), 12 men and 11 women, were evaluated for potential effect of gender (see table below). The overall exposure to drug was 20% higher (C_{max} and AUC) in women compared to that in men. The elimination half-life was 1 hour shorter in women. Since clearances adjusted for body weight were comparable, these small differences are likely related to body weight difference and not to any other inherent difference between genders.

Parameter <i>Gender</i>	C _{max} (µg/ml)	T _{max} (h)	t _{1/2} (h)	AUC _{0-12h} (µg.h/ml)	CL/f (ml/min/kg)	CL _R (ml/min/mg)
Males (N=12)	39±10	0.8±0.4	7.2±0.6	258±35	0.9±0.1	0.6±0.1
Females (N=11)	47±7	0.9±0.8	6.2±0.7	317±40	0.9±0.1	0.6±0.1

Chronopharmacokinetics

During an interaction study of levetiracetam and probenecid (N150), multiple doses (1000 mg b.i.d.) of levetiracetam were given to healthy volunteers before probenecid administration, pharmacokinetic profiles were obtained at steady state. The data from this study for night and day (shown below) do not indicate that there was circadian variability although C_{max} was 20% lower at over-night compared to that over-day.

Parameter	C_{max} ($\mu\text{g/ml}$)	AUC ($\mu\text{g.h/ml}$)	CL/f (ml/min/kg)	CL _R (ml/min/kg)
<i>Circadian</i>				
Day (N=23)	42.8±9.4	286±48	0.88±0.11	0.60±0.13
Night (N=23)	33.4±6.1	265±47	0.95±0.12	0.60±0.11

Pharmacokinetics in Patients with Epilepsy

Is the PK of levetiracetam same in patients with epilepsy as that in healthy subjects?

The pharmacokinetic disposition of levetiracetam characterized in 12 patients (Study N047), who have refractory epilepsy has been found to be consistent with that for healthy volunteers (Study N128). The patients all received at least one other antiepileptic drug in addition to levetiracetam. In both studies, all subjects received multiple doses of 500 mg levetiracetam (2x250 mg capsules) b.i.d. The pharmacokinetic parameters of levetiracetam are summarized below:

Parameter	C_{max} ($\mu\text{g/ml}$)	T_{max} (h)	$t_{1/2}$ (h)	AUC _{0-12h} ($\mu\text{g.h/ml}$)	CL/f (ml/min/kg)
Healthy (N=12)	19.8	1.2	6.4	127	0.94
Epileptic (N=12)	16.9	1.6	6.8	119	1.00

Results from four Phase III studies (N051, N052, N132 and N138) were assessed together in a meta-analysis, and confirm the similarity of levetiracetam pharmacokinetic disposition in healthy volunteers and patients with epilepsy.

Pharmacokinetic Studies in Special Population

Pharmacokinetics in Elderly

Is dosing adjustment necessary for elderly population?

In Study N083 (Belgium), 16 hospitalized elderly subjects (11 women and 5 men, age 77.3±7.8 years) with creatinine clearance (CL_{cr}) ranging from 30 to 74 ml/min were administered single dose (500 mg) and repeated doses (1000 mg/day, b.i.d.) of levetiracetam. Major pharmacokinetic parameters are shown below:

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Parameter	C _{max} (µg/ml)	t _{1/2} (h)	AUC (µg.h/ml)	CL/f (ml/min/kg)	Fe (% Dose)	V _d /f (L/kg)
Single Dose	19.1±0.8	10.3±0.4	251±14	0.60±0.04	46±14	0.52±0.02
Multiple Dose	31.2±1.1	10.4±0.5	248±12	0.60±0.04	75±36	0.53±0.02

In elderly, the elimination half-life is about 2.5 hours longer and plasma clearance is approximately 30% lower compared to that in young adults (t_{1/2}, 7.7 h and CL/f, 0.9 ml/min/kg) mainly due to reduced renal function. Therefore, dosing adjustment is necessary only for elderly with impaired renal function (see Renal Impairment section).

Single Dose in Pediatric Epileptic Patients

Is the PK of levetiracetam same in pediatric population as that in adults?

In Study N151 (United States), 24 pediatric patients (15 male and 9 female, age ranging from 6 to 12 years) suffering from refractory epilepsy with simple and/or complex partial seizures with or without secondary generalization were enrolled. Patients were taking no more than one other AED therapy excluding phenytoin, which they continued in addition to levetiracetam therapy, throughout the study. Although analyses are ongoing, interim results are available for Day 1 after the initial single dose of levetiracetam 20 mg/kg (166.5 mg, 250 mg and 500 mg tablets, titration phase of the study). The following are the major pharmacokinetic parameters for levetiracetam:

Parameter	C _{max} (µg/ml)	t _{1/2} (h)	AUC (µg.h/ml)	CL/f (ml/min/kg)	CL _R (ml/min/kg)	V _d /f (L/kg)
Single Dose	25.8±8.6	6.0±1.1	241±76	1.43±0.36	0.79±0.26	0.71±0.12

In children (6-12 years), the apparent total body clearance is approximately 40% higher than in adults (Studies N069, N143, and N150) and nearly 140% higher than in elderly subjects (Study N083).

Comparison of Levetiracetam PK Parameters in Pediatric, Young and Elderly

The following table summarizes the age effect on pharmacokinetic parameters following a single dose of levetiracetam administration:

Parameter <i>Population</i>	C _{max} (µg/ml)	T _{max} (h)	AUC (µg.h/ml)	t _{1/2} (h)	CL/f (ml/min/kg)	Fe (% Dose)	V _d /f (L/kg)
Pediatric (20mg/kg)	25.8	2.3	241	6.0	1.43	52	0.7
Young (1000mg)	23.0	1.0	222	7.8	1.08	52	0.7
Elderly (500mg)	19.1	1.0	251	10.3	0.60	46	0.5

Pharmacokinetics in Subjects with Renal Impairment

What is the impact of renal impairment on levetiracetam PK?
 Is there any dosage adjustment necessary in this population?
 What special dosing recommendations are being provided?

In Study N137 (Belgium), 10 subjects (5 males and 5 females, age ranging from 40-76 years) received single dose (one tablet of 500 mg) of levetiracetam. Three subjects had normal renal function and the remaining had varying degrees of renal impairment. See attachment (P.14a) for pharmacokinetic parameters. The following table shows the comparison of clearance data between normal and renal impairment:

CL _{cr} (ml/min)	>80 (N=3) (Normal)	50-80 (N=2) (Mild)	30-50 (N=2) (Moderate)	<30 (N=3) (Severe)	R ² *
<i>ucb L059</i>	<i>(Renal Impairment/Normal)</i>				
AUC	1.0	1.7	2.5	3.0	
CL/f	1.00	0.57	0.48	0.35	0.90
CL _R	1.00	0.39	0.23	0.16	0.92
CL _{NR}	1.00	0.73	0.77	0.59	0.37
CL _{NR} /CL	1.00	1.28	1.58	1.65	
<i>ucb L057</i>	<i>(Renal Impairment/Normal)</i>				
AUC	1.00	3.5	6.8	18.3	
CL _R	1.00	0.42	0.25	0.25	0.96

* Correlation coefficient between creatinine clearance and drug clearance.

Study N145 (Sweden) was a follow-up to the previous study and was intended to assess the proposed dosing alterations for subjects with renal impairment. A total of 21 subjects (14 males and 7 females, age of 57.9±17.2 years) completed this study. Five subjects were with normal renal function and the rest subjects had varying degrees of renal impairment. Single and multiple dose (8 days) were administered using a dosage regimen adjusted to renal function (1000 mg/day or 2000 mg/day). See attachment (P.14b) for pharmacokinetic parameters after multiple doses. The following table shows the comparison of clearance data between normal and renal impairment after multiple doses:

CL _{cr} (ml/min)	>80 (N=5) (Normal)	50-80 (N=7) (Mild)	30-50 (N=4) (Moderate)	<30 (N=4) (Severe)	R ² *
		(1000 mg b.i.d.)	(1000 mg b.i.d.)	(500 mg b.i.d.)	
<i>ucb L059</i>	<i>(Renal Impairment/Normal)</i>				
AUC	1.00	1.78	2.50	1.29	
CL/f	1.00	0.59	0.40	0.39	0.89
CL _R	1.00	0.48	0.20	0.17	0.81
CL _{NR}	1.00	0.79	0.77	0.78	0.21
CL _{NR} /CL	1.00	0.78	0.50	0.45	
<i>ucb L057</i>	<i>(Renal Impairment/Normal)</i>				
AUC	1.00	2.64	5.01	6.26	
CL _R	1.00	0.57	0.24	0.14	0.91

*Correlation coefficient between creatinine clearance and drug clearance.

Study N: 137 (Belgium) Single Dose in Renal Impairment

ucb L059 in Renal Impairment Patients

Subject	CLcr	Cmax	Tmax	AUCinf	t1/2	CL/f	CL/f	CLr	CLnr	CLnr/CL
CLcr>80	ml/min	ug/ml	h	ug.h/ml	h	ml/min/kg	ml/min/1.73m ²	ml/min/1.73m ²	ml/min/1.73m ²	%
201	[REDACTED]									
202										
111										
Mean		15.1	0.5	142.2	8.2	0.8	54.5	35.9	23.4	41.0
SD		2.4	0.0	17.2	0.8	0.1	4.6	7.1	10.9	15.6

CLcr50-80

112	[REDACTED]									
221										
Mean		13.9	1.3	243.1	13.6	0.4	31.1	14.1	17.0	55.5
SD		1.8	1.1	29.1	2.3	0.0	3.3	5.5	2.3	13.4

CLcr30-50

121	[REDACTED]									
233										
Mean		14.0	2.5	348.4	15.8	0.4	26.4	8.4	18.0	69.5
SD		2.9	2.1	143.5	1.5	0.1	9.3	4.5	4.8	6.4

CLcr<30

231	[REDACTED]									
232										
142										
Mean		16.7	0.8	424.2	18.6	0.3	19.3	5.6	13.7	72.0
SD		4.2	0.3	102.4	4.8	0.1	4.5	2.7	3.1	12.0

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Study N023 (London) Phase IIb in Renal Impairment

ucb L059 Multiple-Dose in Renal impairment Patients

Subject	CLcr	Cmax	Tmax	AUC12h	t1/2	PTF	CL/f	Ae(0-12)	CLr	CLnr	CLnr/CL
CLcr>80	ml/min/1.73m	ug/ml	h	ug.h/ml	h		ml/min/1.73	(%dose)	l/min/1.73	l/min/1.73	%
195-101											
195-102											
195-103											
195-104											
195-105											
Mean		35.9	1.1	276.4	7.7	1.0	56.0	64.9	36.2	19.8	35.1
SD		3.6	0.8	29.1	0.7	0.1	3.7	10.3	4.8	6.4	10.2

1000 mg b.i.d.

Subject	CLcr	Cmax	Tmax	AUC12h	t1/2	PTF	CL/f	Ae(0-12)	CLr	CLnr	CLnr/CL
CLcr50-80	ml/min/1.73m	ug/ml	h	ug.h/ml	h		ml/min/1.73	(%dose)	l/min/1.73	l/min/1.73	%
195-111											
195-112											
195-113											
195-114											
195-115											
195-122											
195-126											
Mean		54.5	1.4	491.7	12.7	0.7	33.0	50.6	17.3	15.6	49.3
SD		13.0	0.8	161.7	2.4	0.2	7.2	17.4	6.6	3.8	17.3

1000 mg b.i.d.

Subject	CLcr	Cmax	Tmax	AUC12h	t1/2	PTF	CL/f	Ae(0-12)	CLr	CLnr	CLnr/CL
CLcr30-50	ml/min/1.73m	ug/ml	h	ug.h/ml	h		ml/min/1.73	(%dose)	l/min/1.73	l/min/1.73	%
195-121											
195-124											
195-125											
195-131											
Mean		71.2	0.9	690.4	17.1	0.4	22.6	32.3	7.3	15.3	68.0
SD		22.8	0.8	187.4	1.9	0.1	2.6	7.9	2.1	1.7	6.5

500 mg b.i.d.

Subject	CLcr	Cmax	Tmax	AUC12h	t1/2	PTF	CL/f	Ae(0-12)	CLr	CLnr	CLnr/CL
CLcr<30	ml/min/1.73m	ug/ml	h	ug.h/ml	h		ml/min/1.73	(%dose)	l/min/1.73	l/min/1.73	%
195-133											
195-132											
195-134											
195-135											
195-143											
Mean		36.6	0.5	356.8	19.3	0.4	21.7	28.9	6.2	15.5	71.1
SD		8.0	0.0	73.4	1.1	0.0	2.9	9.4	1.8	3.7	9.2

9/2/12

Pharmacokinetic parameters following multiple administration were well predicted from the single dose data. Results of both single dose and multiple dose renal impairment studies show that clearance decreased by 40% in mild, and by 60% in both moderately and severely renally impaired patients. The metabolite ucb L057 produced via levetiracetam metabolism was increased and its renal clearance decreased.

Total body clearance of levetiracetam and renal clearances of the parent drug and the metabolite ucb L057 were well correlated with CL_{Cr} (see P.15a,b for the plots). Therefore, the CL_{Cr} can serve as a guide to modify dosage regimens of levetiracetam in the renal impairment patients. Based on these two studies, an adjustment of the daily maintenance dose is proposed as follows:

Group Renal Function	Creatinine Clearance (ml/min)	Dosage (mg)	Frequency
Normal	>80	500 to 1,500	Every 12 h
Mild			
Moderate	30-50	250 to 750	Every 12 h
Severe			

Patients Undergoing Hemodialysis

Are levetiracetam and ucb L057 removable through dialysis unit?
What should be the dosage adjustment?

Study N152 (Belgium) in five anuric end stage renal disease (ESRD) subjects (2 males and 3 females, mean age of 58.4 years) was conducted to examine the dialyzability, dialysis clearance, and pharmacokinetics of levetiracetam and its major metabolite ucb L057. Plasma samples were collected over the 5-day study period following dosing (500 mg of levetiracetam) after a 4-hour dialysis session (see attached figure, P.15c). Major pharmacokinetic parameters of levetiracetam are shown below:

Parameter	C _{max} (µg/ml)	t _{1/2} (h)	AUC (µg.h/ml)	CL/f(ml/min/1.73m ²)	Vd/f (L/kg)
Mean±SD	15.5±3.5	24.6±7.8	517±253	18.2±7.2	0.5±0.1
Dialyzability and Hemodialysis Clearance					
			Levetiracetam	ucb L057	
Dialyser Extraction Efficiency (%)			59.7±5.0	73.5±5.6	
Fraction removed (%)			51.0±5.8	---	
T _{1/2} during hemodialysis (h)			3.1±0.5	2.7±0.5	
Hemodialysis clearance (ml/min/1.73m ²)			127±17	99±10	

The clearance of levetiracetam in anuric ESRD subjects was only 30% of that in healthy subjects. The half-life of levetiracetam on inter-dialysis periods averaged 25 hours as compared to 3.1 hours during intra-dialysis periods. Approximately 50% of levetiracetam was removed during a typical 4-hour dialysis session.

Single dose pharmacokinetics of orally administered 500 mg of ucb L059 in subjects with mild, moderate or severe renal impairment or with normal renal function

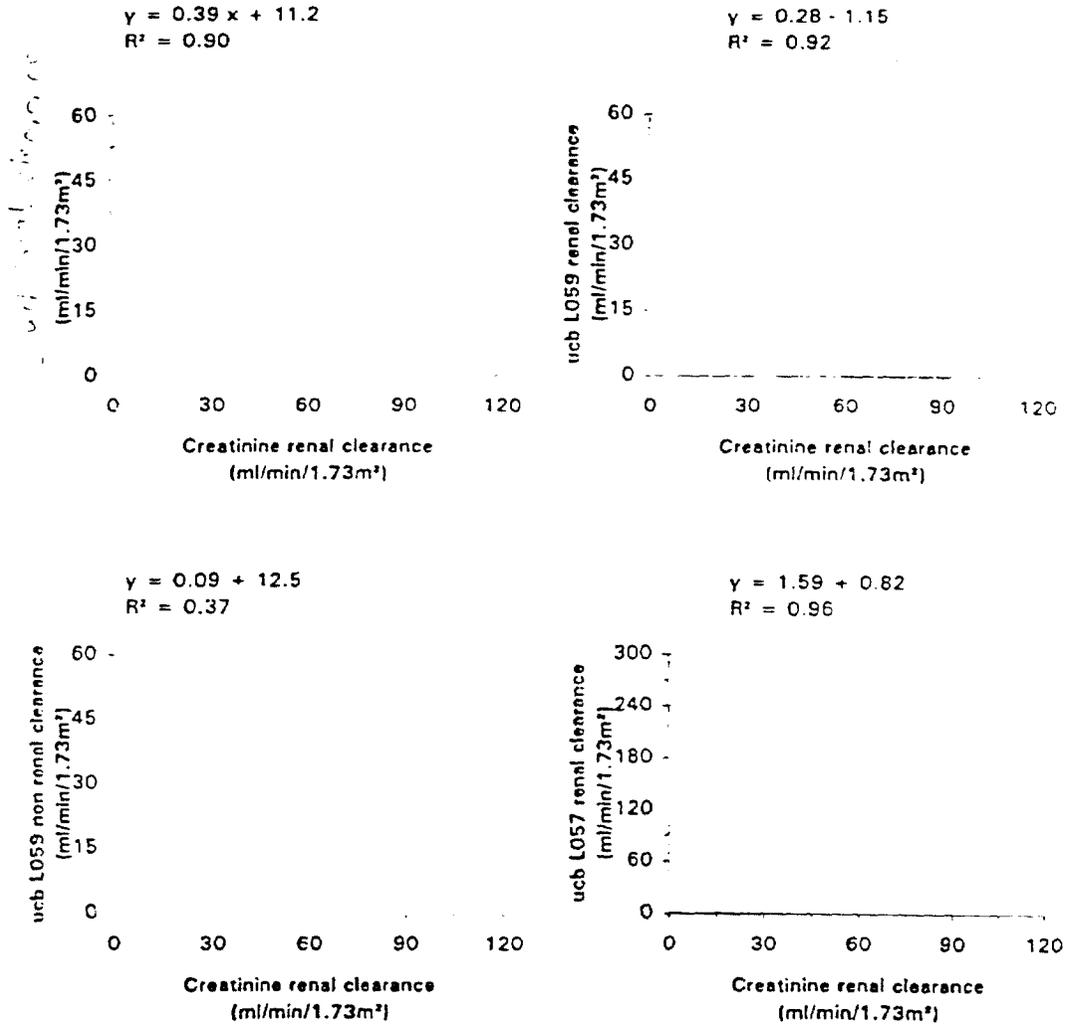


Figure 3

Total Body Clearance (Top Left), Renal Clearance (Top Right) and Non Renal Clearance of ucb L059 (Bottom Left) And Renal Clearance of ucb L057 (Bottom Right) as a function of the Renal Clearance of Creatinine.

Data were equated for a Body surface Area of 1.73 m² and were available from 5 females and 5 males. Subject No. M111 was not used for trendline estimate of renal clearance of ucb L059 and ucb L057 as a function of creatinine clearance (anomalous high urinary excretion).

Multiple Dose

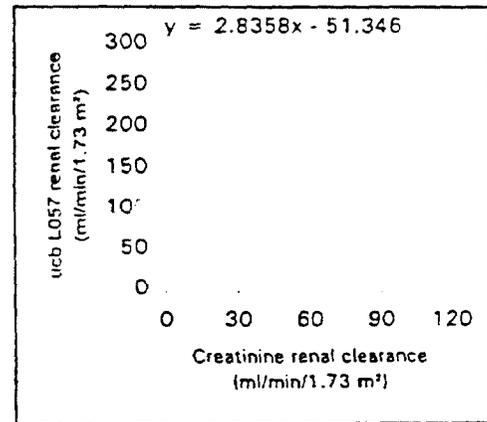
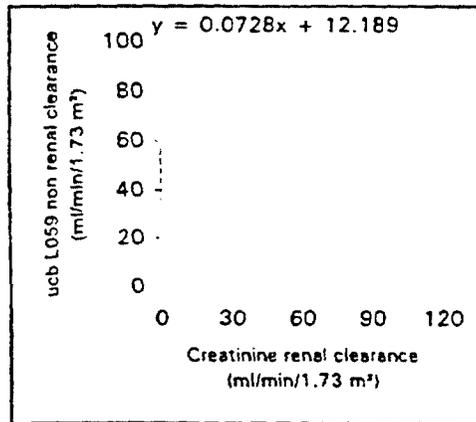
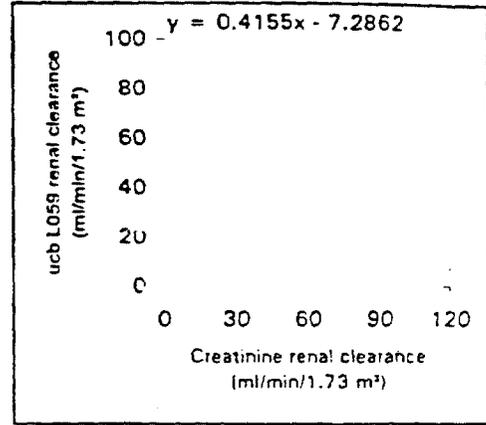
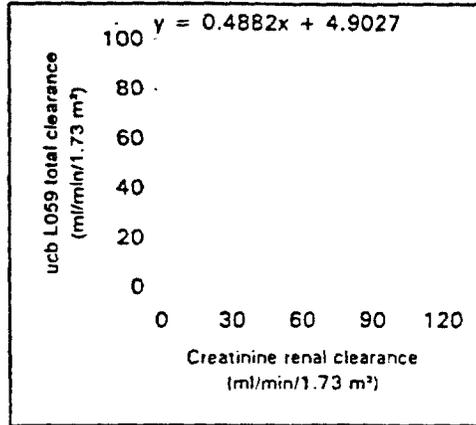
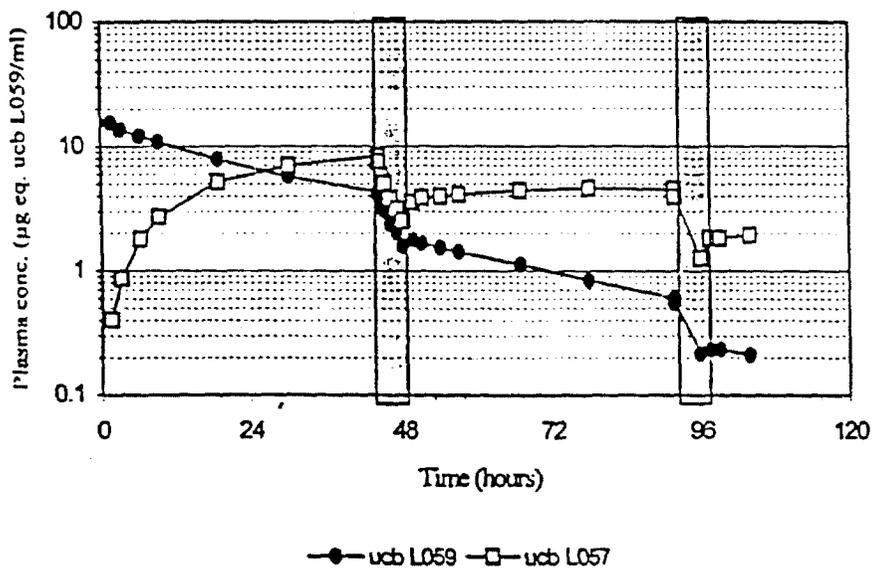


Figure 11.4.1.4.A - Total body clearance (top left), renal clearance (top right) and non renal clearance of ucb L059 (bottom left) and renal clearance of ucb L057 (bottom right) as a function of the renal clearance of creatinine, following multiple oral administration of ucb L059 at target doses adjusted according to the renal impairment. Data were equated for a body surface area of 1.73 m².

Individual data including plasma levels, urinary excretion and pharmacokinetic parameters are presented in Addendum 1, separately for single dose and multiple dose information. Statistical evaluation for pharmacokinetic data, quality control and calibration measurements are also presented in Addendum 1.

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Plasma concentrations-time profile of ucb L059 and ucb L057 in end-stage renal insufficiency subjects undergoing haemodialysis (mean of 2 males and 3 females).

Data are presented in semi-log scale. Shaded areas represent the dialysis sessions

- In anuric ESRD subjects, the absorption of ucb L059 was rapid and complete and the half-life assessed during non-haemodialysis periods was 25 hours. The CL/f was close to the CL_{NR} (non renal clearance) reported in healthy volunteers and mild or moderate renal impaired subjects. The apparent volume of distribution also does not differ from that generally reported.

0.50

It is recommended that naive ESRD patients maintained on hemodialysis receive 500 to 1000 mg dose every 24 hours as the clearance of levetiracetam in these patients was only 30% of that in healthy subjects. Following dialysis, a 250 to 500 mg supplemental dose should be administered because the dialysis unit removes 50% of levetiracetam dose.

Pharmacokinetics in Subjects with Hepatic Impairment

What is the impact of hepatic impairment on levetiracetam PK?
Is there any dosage adjustment necessary in this population?

In Study N139 (Germany), 4 groups (21 male subjects) received a single dose of 1000 mg (2x500mg) of levetiracetam. Group 1 included 5 subjects with normal liver function and the other three groups were composed of subjects with chronic liver cirrhosis of alcoholic etiology, and were classified by their degrees of liver impairment. The levetiracetam clearance data are listed below:

Parameters	Healthy	Child-Pugh A	Child-Pugh B	Child-Pugh C
CL _{cr} (ml/min)	93±14	121±12	100±13	63±13
<i>ucb L059</i>	<i>N=5</i>	<i>N=5</i>	<i>N=6</i>	<i>N=5</i>
CL/f (ml/min/1.73m ²)	63±10	63±9	55±11	29±14
CL _R (ml/min/1.73m ²)	44±11	42±9	34±8	17±11
CL _{NR} (ml/min/1.73m ²)	19.3±1.8	20.1±4.7	21.2±5.0	12.4±2.5
CL _{NR} /CL (%)	31±7	33±8	38±7	46±10
<i>ucbL057</i>				
CL _R (ml/min/1.73m ²)	230±24	270±62	251±52	116±43

It would appear that dosage reduction would be recommended for the patients with severe hepatic impairment as their total clearance decreased two-fold compared to healthy subjects. However, their non renal clearance decreased by only 36% and the ratio of CL_{NR}/CL was not decreased in these subjects. These data indicate that the role of the liver in the metabolism of levetiracetam is limited. A reduction in the daily maintenance dose of levetiracetam would be recommended for patients with severe hepatic impairment and with concomitant renal impairment.

Formal Drug Interaction Studies

Oral Contraceptives

Is there any drug-drug interaction between levetiracetam and oral contraceptives?

Study N135 (Germany) consisted of four, 21-day periods. During the first two run-in periods, subjects received only Microgynon[®]21 (ethinylestradiol 0.03mg/levonorgestrel 0.15mg), once daily for 21 days of their cycles. In each of the second two treatment periods, subjects were randomized in a double blind, crossover fashion to receive either levetiracetam (500 mg, Treatment A) or placebo (Treatment B) twice daily in addition to

Microgynon®21 once daily for 21 days. The major pharmacokinetic parameters are shown below:

Parameter N=18	AUC ₀₋₂₄ (pg.hr/ml)	C _{max} (pg/ml)	C _{min} (pg/ml)	C _{ave} (pg/ml)	T _{1/2} (hr)
<i>Ethinylestradiol</i>					
Treatment A	1020±259	123±51	14±8	43±11	10.8±2.9
Treatment B	1019±247	123±43	14±8	42±10	10.8±2.3
Parameter	AUC ₀₋₂₄ (pg.hr/ml)	C _{max} (ng/ml)	C _{min} (ng/ml)	C _{ave} (ng/ml)	T _{1/2} (h)
<i>Levonorgestrel</i>					
Treatment A	92±40	8.2±3.2	2.3±1.0	3.8±1.7	28.3±11.1
Treatment B	96±44	8.7±3.7	2.4±1.2	4.0±1.8	24.9±6.7
Parameter N=18	AUC ₀₋₁₂ (µg.h/ml)	C _{max} (µg/ml)	C _{min} (µg/ml)	C _{ave} (µg/ml)	T _{1/2} (h)
<i>ucb L059</i>					
Treatment A	141±20	20.8±1.9	5.2±1.3	11.8±1.7	5.5±0.8

Levetiracetam did not affect Microgynon®21 as evidenced by the comparative pharmacokinetic parameters for ethinylestradiol and levonorgestrel (90% CI for C_{max} and AUC₀₋₂₄ ratios lie within 0.80-1.25). The pharmacokinetics of levetiracetam was consistent with the results of other studies in which no other medication was administered indicating that Microgynon®21 does not influence the disposition of levetiracetam.

Digoxin

Is there any drug-drug interaction between levetiracetam and digoxin?
Is digoxin pharmacodynamics affected by levetiracetam?

In Study N144 (Germany), steady state was achieved by treating 11 healthy volunteers (7 males and 4 females) with digoxin (0.25mg/day) only for an 8-day run-in period. Subjects were then randomized in a double blind, crossover fashion to receive either levetiracetam (2x500 mg tablets, 2000mg/day, b.i.d.) or placebo in addition to digoxin therapy for each of two 7-day treatment periods. There was no washout between treatment periods. The major pharmacokinetic and pharmacodynamic parameters are listed below:

Parameter N=11	AUC _{ss} (ng.h/ml)	C _{max} (ng/ml)	C _{min} (ng/ml)	C _{ave} (ng/ml)	T _{max} (hr)
<i>Digoxin</i>					
Treatment A	17.4±3.1	1.7±0.4	0.5±0.1	0.7±0.1	1.0
Treatment B	16.6±2.5	1.7±0.3	0.5±0.1	0.7±0.1	1.0
Treatment C	15.8±2.6	1.5±0.3	0.4±0.1	0.7±0.1	1.0
Parameter N=11	0-12h (µg.h/ml)	C _{max} (µg/ml)	C _{min} (µg/ml)	C _{ave} (µg/ml)	T _{max} (hr)
<i>ucb L059</i>					
Treatment B	265±50	35.8±6.6	11.9±2.5	22.1±4.1	1.0

ECG	P-R Interval (msec)	Q-T Interval (msec)	T-height (mv)	QRS Interval (msec)
Treatment A	161±17	376±20	0.21±0.08	92±9
Treatment B	158±19	366±36	0.19±0.01	87±9
Treatment C	152±15	370±17	0.23±0.1	88±9

Treatment A (digoxin + ucb L059), Treatment B (digoxin + placebo), Treatment C (digoxin alone).

For pharmacokinetics of digoxin, all 90% confidence intervals on ratios were fully contained in the interval between 80 and 125%. Therefore, the coadministration of levetiracetam and digoxin does not lead to a clinically relevant drug-drug interaction with respect to the pharmacokinetics and pharmacodynamics (ECG values) of digoxin.

Based on a cross study comparison, levetiracetam pharmacokinetic parameters were comparable indicating that digoxin does not influence the pharmacokinetics of levetiracetam.

Warfarin

Is there any drug-drug interaction between levetiracetam and warfarin?
Does levetiracetam displace warfarin from its plasma protein binding sites?
Is warfarin pharmacodynamics affected by levetiracetam?

In Study N146 (Germany), warfarin was given in once daily doses of 2.5 mg, 5.0 mg, or 7.5 mg as needed to 26 healthy volunteers (18 males and 8 females, ages 18 to 50 years) to maintain PT within the designated range (1.3 to 2.0). At the start of the treatment periods (Day 1), subjects were randomized to receive either levetiracetam (2x500 mg tablets, 2000mg/day, b.i.d.) or placebo in addition to their stable daily warfarin dose. The treatment periods were 7 days long and were separated by a 3-day washout period during which patients maintained their warfarin dosage regimen. The major pharmacokinetic and pharmacodynamic parameters are shown below:

Parameter N=26	AUC _{ss} (µg.hr/ml)	C _{max} (µg/ml)	C _{min} (µg/ml)	PTF (%)	CL/f (ml/min)
<i>Total RS-warfarin</i>					
Treatment A	22.4±4.6	1.3±0.3	0.7±0.2	68±22	3.4±0.8
Treatment B	22.9±5.9	1.3±0.2	0.7±0.2	64±15	3.3±0.8
Treatment C	22.8±5.7	1.3±0.3	0.7±0.2	66±18	3.4±0.8
<i>ucb L059</i>			C _{ave}	T _{1/2} (h)	(ml/min/kg)
Treatment B	258±51	34.0±6.4	21.5±4.3	6.7±1.0	0.9±0.1

Treatment	Treatment A	Treatment B	Treatment C
INR	1.55±0.23	1.49±0.21	1.59±0.18
% Binding	99.2±0.1	99.2±0.1	99.2±0.1

Treatment A (warfarin + ucb L059), Treatment B (warfarin + placebo), Treatment C (warfarin alone). INR: International Normalized Ratio.

The 90% confidence intervals for the geometric ratios of pharmacokinetic parameters for S-warfarin, R-warfarin, and RS-warfarin were within [redacted] Warfarin plasma protein binding and the prothrombin time were not affected by levetiracetam.

Pharmacokinetic values of levetiracetam in the presence of warfarin agree with those obtained in subjects receiving multiple doses of levetiracetam (Study N128, and Study N145) without taking any other medications.

In conclusion, the coadministration of levetiracetam and warfarin does not lead to a clinically relevant drug-drug interaction.

Probenecid

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What would be the impact of a renal tubular secretion blocking drug on levetiracetam disposition?
Does the interaction lead to dosing adjustment?

Study N150 (U.K.) was a two-period crossover study with a 14-day washout period. During the treatment periods, 23 healthy volunteers (12 males and 11 females) were randomized to receive either levetiracetam (2x500 mg tablets, 1000 mg b.i.d. for 4 days) alone or levetiracetam at the same dose plus probenecid (500 mg q.i.d.) starting concurrently and continuing for 7 days. The major pharmacokinetic parameters of levetiracetam (ucb L059) and its metabolite (ucb L057) are shown below:

Parameter N=23	AUC ₀₋₁₂ (µg.hr/ml)	C _{max} (µg/ml)	T _{max} (hr)	T _{1/2} (hr)	CL/f (ml/min/kg)	CL _R (ml/min/kg)
<i>ucb L059</i>						
Alone	286±48	42.8±9.4	0.9±0.6	6.7±0.8	0.9±0.1	0.6±0.1
Combination	279±46	42.8±8.2	0.8±0.4	6.4±0.9	0.9±0.1	0.6±0.2
<i>ucb L057</i>						
				fe (0-12h) (%)		
Alone	11.4±2.7	1.3±0.3	3.7±1.1	22.2±6.4		4.9±1.2
Combination	30.2±8.3	2.9±0.8	4.1±1.6	22.0±5.2		1.9±0.5

The rate and extent of exposure of levetiracetam and its renal clearance observed at steady state in this study agree closely with the results of other studies. Also, the values obtained in this study were not affected by probenecid administration. C^{ss}_{max} (ucb L057) was approximately 2.2-fold in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%. This effect was likely to be related to competitive inhibition of tubular secretion of ucb L057. No dosing adjustment is necessary.

The effect of levetiracetam on the pharmacokinetics of probenecid was not studied.

Phase III Drug Interaction Studies

Phase III epilepsy studies (Studies N051, N132, N138 and N052)

Meta-analysis

What is the most important drug-drug interaction that we should be concerned with?
Do the interactions lead to any dosing adjustment?

The main clinical concern would be does levetiracetam increase the levels of existing anti-epileptic drugs (AEDs) such as carbamazepine, phenytoin, valproic acid, lamotrigine, gabapentin, phenobarbital and primidone. A meta-analysis to assess the potential for pharmacokinetic 2-way drug interactions between levetiracetam and other anti-epileptic drugs (AEDs) was performed with data from 4 placebo-controlled Phase III clinical studies (Studies N051, N132, N138 and N052) in 1023 epilepsy patients taking one or more concomitant AEDs (see P.20a for study designs). Serum concentrations of eight co-administered AEDs (carbamazepine, phenytoin, valproic acid, lamotrigine, gabapentin, phenobarbital, primidone and vigabatrin) with constant doses were collected by sparse sampling (pharmacokinetic screen). The average concentrations of AEDs with levetiracetam or with placebo are shown below:

AED	<i>With Levetiracetam</i>			<i>With Placebo</i>	
	N	E _{I-III} (B) C (µg/ml)	Ratio (90% CI)	N	E _{I-III} (B) C (µg/ml)
Carbamazepine	368	8.6 (8.7)	0.98 (0.96-1.01)	212	8.5 (8.5)
Phenytoin	109	14.4 (14.0)	0.99 (0.83-1.04)	65	13.7 (14.3)
Valproic Acid	118	71.6 (75.2)	0.94 (0.90-1.03)	56	69.0 (68.1)
Lamotrigine	48	6.0 (6.2)	0.98 (0.92-1.13)	25	6.4 (6.0)
Gabapentin	57	6.7 (6.6)	0.98 (0.88-1.11)	22	7.0 (6.2)
Phenobarbital	44	27.0 (26.5)	1.01 (0.96-1.14)	30	26.5 (24.4)
Primidone	20	10.7 (11.2)	0.95 (0.89-1.16)	15	9.3 (8.1)
Vigabatrin	12	12.5 (13.6)	0.88 (0.67-1.42)	9	12.4 (12.0)

B is baseline and E_{I-III} is evaluation session I to III. C represents mean concentrations at baseline and at evaluation sessions I to III.

See P.20b for the plot of Ratios of geometric means of individual AEDs as assessed during all evaluation sessions combined compared to baseline. Also see P.20c for the plot of comparative levels of exposure to levetiracetam in Phase III clinical studies and in other pharmacokinetic studies.

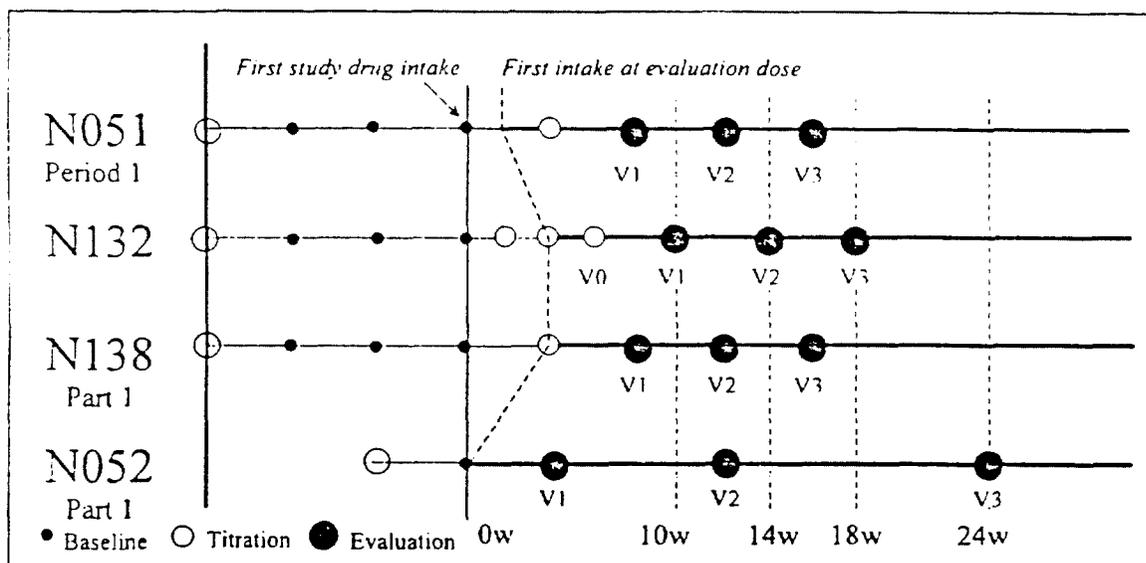
Based on the analysis, levetiracetam neither increases nor decreases the steady-state serum concentrations of carbamazepine, phenytoin, valproic acid, lamotrigine, gabapentin, phenobarbital and primidone in patients receiving constant doses of these AEDs. For vigabatrin, the 90% confidence interval was outside the acceptable range because of paucity of data since no serum concentration data were available in a large number of patients (up to 76%) using vigabatrin therapy.

levetiracetam or placebo. However, the elapsed time between time of last intake and sampling time was variable and ranged from 0 to more than 12 hours.

Study drug was to be given twice a day with a time interval of 12 hours between sub-doses. Daily maintenance doses were either placebo, 1000 mg or 2000 mg in Study N051; placebo, 1000 mg or 3000 mg in Study N132; placebo or 3000 mg in Study N138; and placebo, 2000 mg or 4000 mg in Study N052. Doses and administration schedule of AED's for all individual patients was not modified when study drug was added to treatment.

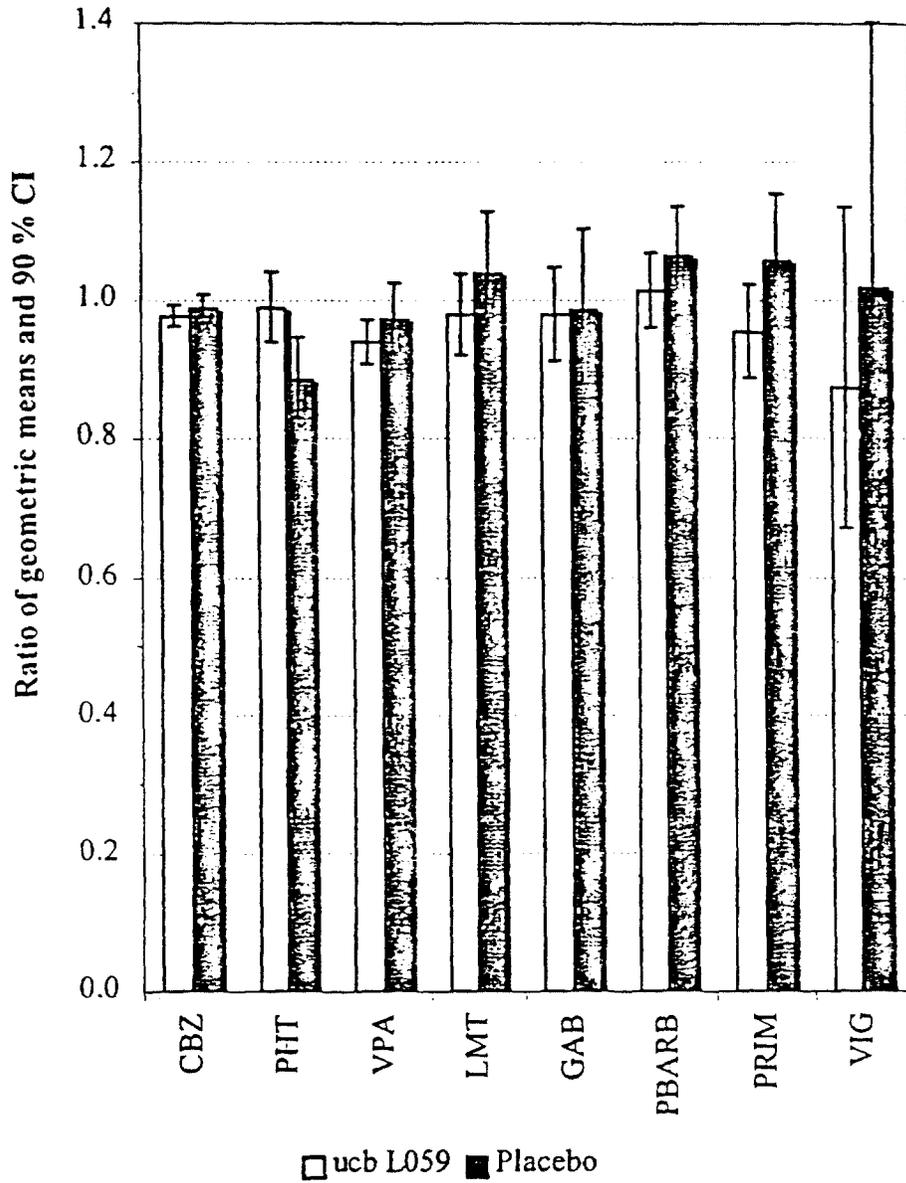
5.2. Brief description of studies

Only those periods used for the assessment of drug-drug interactions are described here after. Flow charts are provided in Section 11.4 (Statistical Analysis Plan). A summary of study designs is given below.



	Plc	L059 1g	L059 2g	L059 3g	L059 4g	Evaluation weeks number	Evaluation Visit number	Comments
N051	X	X	X			20, 24, 28	6, 7, 8	First period only
N132	X	X		X		22, 26, 30	8, 9, 10	
N138	X			X		20, 24, 28	6, 7, 8	DB add-on part only
N052	X		X		X	4, 12, 24	3, 4, 5	DB part only

Assessment of pharmacokinetic drug-drug interactions in levetiracetam phase III epilepsy studies (meta-analysis)



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Figure 4

Ratios of geometric means of individual AEDs as assessed during all evaluation sessions combined compared to baseline concentrations taken as reference. Bars represent 90% CI intervals.

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 Assessment of pharmacokinetic drug-drug interactions in levetiracetam phase III epilepsy studies
 (meta-analysis)

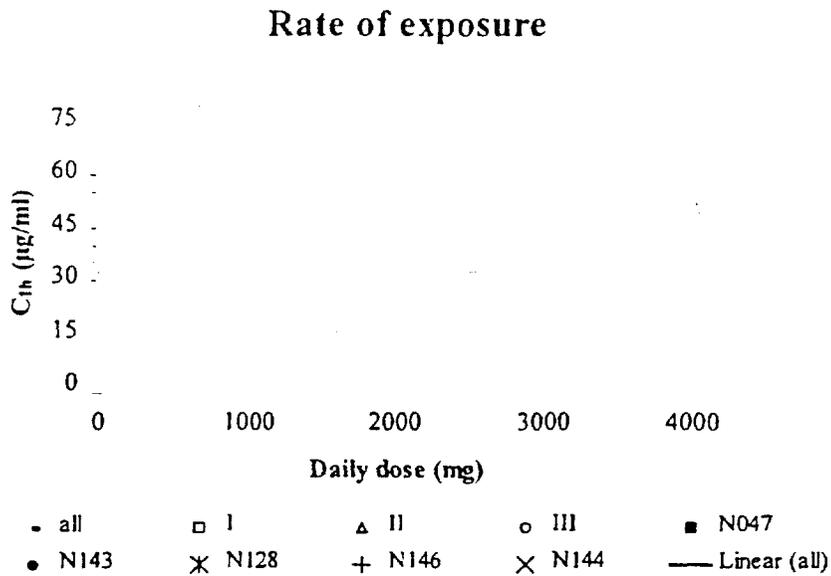
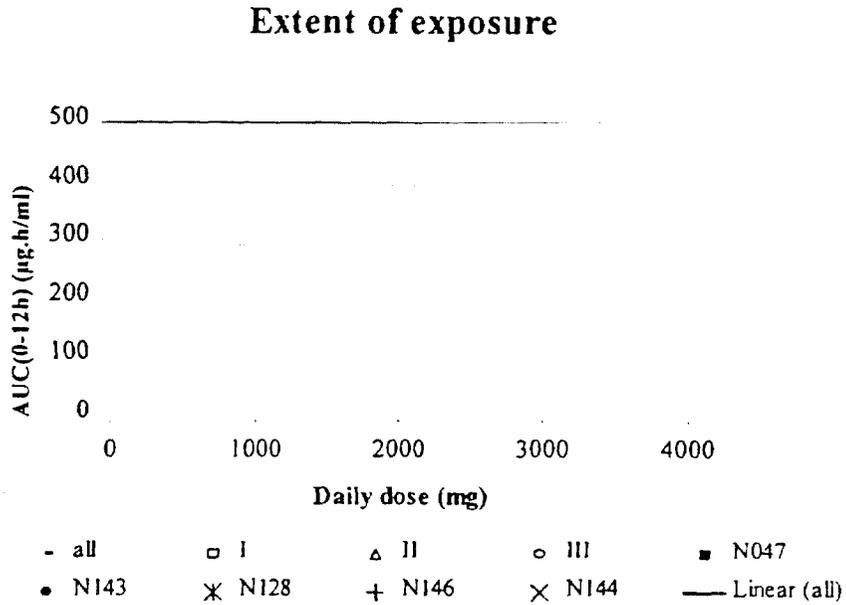


Figure 5

Comparative levels of exposure to levetiracetam in Phase III clinical studies and in pharmacokinetic studies (historical data).

Mean C_{0-12h} for N143, $C_{1.5h}$ for N047, C_{1h} for N128 & N144, $C_{1.5h}$ for N146 were used.

I, II and III represent the data of three consecutive evaluation sessions; "all" contains the data of the three evaluation sessions combined. Linear (all) is the regression line calculated from mean values of either $AUC_{(0-12h)}$ or C_{1h} available at each dose level for the three evaluation sessions.

Levetiracetam plasma concentrations measured at each evaluation session were used to calculate pharmacokinetic variables ($T_{1/2}$, C_{1h} , C_{12h} and $AUC_{(0-12h)}$). Log-transformed dose adjusted concentrations were used to calculate the regression line as a function of elapsed time for all available data and for several subgroups of data. This includes time effects over the evaluation period, dose effects, gender effects and category of concomitant AED's effects (inducers, inhibitors and others). The concentrations were dose adjusted (concentration/dose in mg/kg) for each individual patient prior to log transformation. The parameters for all evaluation sessions combined are shown below:

Dose	N	C_{1h} ($\mu\text{g/ml}$)	C_{12h} ($\mu\text{g/ml}$)	$AUC_{(0-12h)}$ ($\mu\text{g}\cdot\text{h/ml}$)	$t_{1/2}$ (h)
1g	182	14.9	5.8	122	8.1
2g	121	23.4	9.9	197	8.8
3g	258	43.4	16.8	354	8.1
4g	29	49.6	19.2	404	8.0
Category					
All	590				8.2
Inducers ^a	325				7.9
Inhibitors ^b	46				11.6
Others	28				8.6

^a Inducers included carbamazepine, phenytoin, phenobarbital and primidone. ^b Valproic acid is considered an inhibitor. Others included vigabatrin, gabapentin and lamotrigine.

The pharmacokinetic variables of levetiracetam were similar to those in the formal studies in epileptic patients (N143 and N047) and in healthy volunteers (N128, N144 and N146). The half-life of levetiracetam was independent of the duration of treatment and of the dose. There was no evidence suggesting a shorter half-life in patients receiving concomitant AEDs known to be inducers (carbamazepine, phenytoin, phenobarbital, and primidone).

In conclusion, these data confirm that levetiracetam is unlikely to affect the pharmacokinetics of concomitant AEDs either by inducing or by inhibiting their elimination. Also, the pharmacokinetics of levetiracetam is not affected by the concomitant AEDs.

In Vitro Enzymatic Interaction

Metabolism

What is the major metabolic pathway?
What enzymes are involved and where are they located?

In vitro metabolism studies were conducted to investigate the hydrolysis of the acetamide group giving rise to the major human metabolite, ucb L057. This metabolite was formed following incubation (for 1 hr at 37°C) of levetiracetam (at 25 or 500 $\mu\text{mol/l}$, i.e., 4 or 85 $\mu\text{g/ml}$) with human whole blood and liver fractions and all rat tissue homogenates. Whole

blood samples were the most active in hydrolyzing levetiracetam, followed by liver homogenates, and then by plasma fractions (mean activity of 3.3, 0.29 and 0.04 $\mu\text{mol/l/h}$, respectively). Addition of NADPH has no effect on formation of ucb L057, suggesting CYPs are not involved. No ucb L057 was detected in the absence of active tissue homogenates. These data indicate hydrolysis of levetiracetam into ucb L057 is supported by an enzymatic process with a broad tissue distribution.

Enzymatic Interaction

Are levetiracetam and its major metabolite, ucb L057 potential liver enzyme inhibitors or inducers?

The potential of levetiracetam to produce metabolic interactions was evaluated using a panel of *in vitro* inhibition assays with human liver microsomes. It was demonstrated that levetiracetam and ucb L057 at concentrations up to 170 $\mu\text{g/ml}$, well above C_{max} concentrations following repeat therapeutic doses are neither inhibitors of nor high affinity substrates for human liver cytochrome P-450 isoforms (CYP1A2, CYP2A6, CYP2C8/9/10, CYP2C19, CYP2D6, CYP2E1, and CYP3A4), epoxide hydrolase and UDP-glucuronidation enzymes belonging to UGT1*1, UGT1*6 and UGT families. *In vitro*, levetiracetam up to 170 $\mu\text{g/ml}$, does not induce CYP marker activity or CYP proteins in human hepatocytes.

Inhibition

In vitro metabolic studies using human microsomal fractions have shown that levetiracetam and its major metabolite (ucb L057) at concentrations as high as 170 $\mu\text{g/ml}$, did not inhibit the following enzymes: R-warfarin 6-hydroxylation (CYP1A2), coumarin hydroxylation (CYP2A6), tolbutamide hydroxylation (CYP2C8/9/10), S-mephenytoin 4'-hydroxylation (CYP2C19), dextromethorphan O-demethylation (CYP2D6), p-nitrophenol hydroxylation (CYP2E1), - testosterone 6 β -hydroxylation (CYP3A), R-warfarin 10-hydroxylation (CYP3A4), styrene oxide hydrolase, glucuronidation of valproic acid, of paracetamol (UGT1*6), of ethinylestradiol (UGT1*1) and of p-nitrophenol (UGT p16.2). The *in vitro* data indicate that levetiracetam is unlikely to produce pharmacokinetic interactions through inhibition of liver drug metabolizing enzymes.

Induction

In vitro metabolic studies have shown that at concentrations up to 170 $\mu\text{g/ml}$, following a 72-hour incubation in primary cultures of human hepatocytes, levetiracetam did not increase the activities of 7-ethoxyresorufin O-deethylase (CYP1A1/2), chlorzoxazone hydroxylase (CYP2E1) and midazolam hydroxylase (CYP3A4). Moreover, the CYP proteins were not affected, as assessed by Western blot analyses.

