CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-872

PHARMACOLOGY REVIEW

January 20, 2006

Review and Evaluation of Pharmacology and Toxicology

NDA: 21-872

Sponsor: UCB Pharma
Smyrna, GA

Received: December 20, 2004

Drug: Keppra (levetiracetam) injection

Category: Parenteral antiepileptic

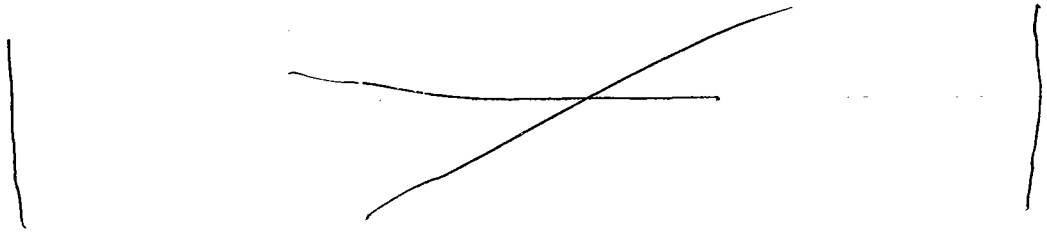
Related INDs and NDAs: INDs 45,151 and 68,187; NDAs 21-035 and 21-505

Background: The only significant new pharmacology/toxicology data submitted with this NDA are reports from cardiovascular safety pharmacology studies in vivo (oral and iv in dogs) and in vitro (dog purkinje fibers, dog and human blood) and single and repeated dose (up to 1-month) iv toxicity studies in rats and dogs. It was previously agreed that studies of this duration in two species would suffice for this injectable form of levetiracetam, which is intended as replacement therapy when oral therapy with levetiracetam is not possible.

Studies:

I. Cardiovascular effects of ucb L059 following single oral capsule administration in conscious dogs (RRLE99M0301; UCB study #TA0578; conducted by [redacted] report dated 2/00; GLP)

A) Methods



B) Results

At a dose of 600 mg/kg, a transient but statistically significant (SS) increase in heart rate (+34% of predose mean at I hr post dosing) and a decrease in QT interval duration (-11% of predose mean at 1 hour post-dosing) were seen. There were no SS changes in mean, systolic and diastolic blood pressures, PR interval, or QRS duration at this dose. No SS changes (arterial blood pressure, heart rate, PR and QT intervals, QRS complex duration) were seen at the lower doses. QT interval corrected for heart rate did not show any SS change at any dose. No other

disturbances of the electrocardiogram (Lead II over 24-hour period post-dosing and leads I, II, III, aVL and aVF, 3 hours after dosing) and no alteration of the T wave morphology attributable to treatment were seen at any dose (ie 150, 300 and 600 mg/kg).

Vomiting was seen in 2 (1 male and 1 female) HD dogs, 40 minutes and 3 hours after dosing, and in 1 MD (male) dogs, 30 minutes after dosing. There were no other clinical signs reported.

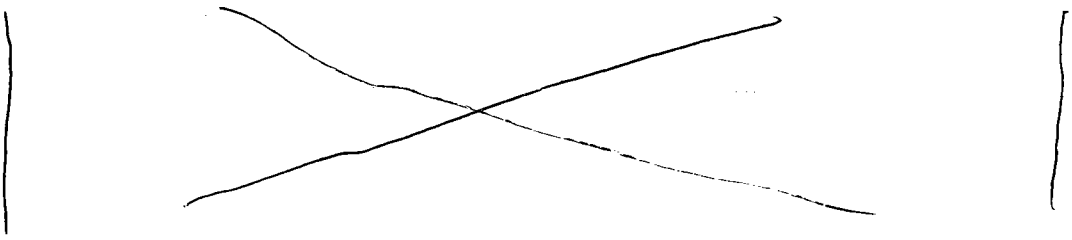
Plasma concentrations (only 3 hr) of the parent drug appeared to be linearly dose-related and similar for males and females: concentrations (males and female combined) were 160 ± 15, 303 ± 34 and 507 ± 63 ug/ml at the LD, MD, and HD, respectively. Concentrations of the metabolite were less than proportional: concentrations were 3.31 ± 0.65, 4.84 ± 0.86 and 5.78 ± 0.99 ug eq. ucb L059/ml.

C) Conclusions

Administration of a single (oral capsule) dose of 600 mg/kg (associated with 3 hr plasma level of 500 ug/ml) produced a transient increase in heart rate with shortening of the QT interval. However, the QT corrected for heart rate was unchanged. Vomiting was observed at ≥300mg/kg. Notably, pulmonary arterial pressure was not measured in this study.

II. Effect of ucb 059 on cardiovascular and respiratory function parameters following iv administration in anesthetized dogs (RRLE97E1403; UCB study #TA0358; conducted by [redacted] report dated 5/98; GLP)

A) Methods



B) Results

There was a dose-related increase in pulmonary artery pressure following iv administration of drug at all doses tested (maximally 2-4-fold pre-drug levels; seen in 2/4, 4/4, and 4/4 dogs at the respective doses; Table II.1). The maximal effect was generally seen within 5 minutes of drug administration, with values returning to baseline over the next 15 minutes. There were treatment-related effects on any of the other measured or derived parameters following treatment with vehicle or ucb L059 at any of the doses tested with the exception of a small decrease in left ventricular dp/dt maximum at 450 mg/kg (NS compared compared to vehicle control).

Plasma concentrations in samples taken approximately 45 minutes after administration were 57.8, 208 and 634 ug/ml at the LD, MD, and HD, respectively. Peak concentrations at these doses and infusion time are not known. The Cmax in humans at the end of a single 15-min infusion of 1500 mg is reportedly about 50 ug/ml. (A human Cmax of 81 ug/ml was reported after a 15 min iv infusion of 3000 mg and a Cmax of 94 ug/ml was seen after a 5 min infusion of 2500 mg.)

C) Conclusions

Intravenous administration (5 min infusion; 2.5 ml/kg) of 50, 150 and 450 mg/kg levetiracetam produced a transient, dose-related elevation of pulmonary artery pressure in the anesthetized dog. No notable effects on any of the other measured cardiovascular or respiratory parameters were seen, with the possible exception of a slight decrease in left ventricular dp/dt maximum at 450 mg/kg.

Table II.1

The group mean maximum percentage changes in mean pulmonary artery pressure following intravenous administration of vehicle or ucb L059

Treatment and dose (mg/kg) i.v.	Group mean maximum percentage changes ± s.e.m. from immediately pre-dose
	Mean pulmonary artery pressure
Vehicle dose 1 (2.5 ml/kg)	4.65 ±10.84
Vehicle dose 2 (2.5 ml/kg)	-0.33 ±5.51
Vehicle dose 3 (2.5 ml/kg)	5.50 ±8.30
Vehicle dose 4 (2.5 ml/kg)	0.20 ±5.21
Vehicle (2.5 ml/kg)	7.08 ±7.20
ucb L059 (50 mg/kg)	30.15* ±8.63
ucb L059 (150 mg/kg)	98.40* ±32.18
ucb L059 (450 mg/kg)	178.50* ±60.17

n = 4
Changes are calculated with reference to the value 1 minute prior to the relevant dose
Significance of difference compared with vehicle using Student's *t* test: * $p<0.05$
s.e.m. Standard error of mean

III. Effects of ucb L059 on pulmonary arterial pressure and blood parameters following single intravenous administration in conscious dogs (RRLE98L1201; UCB study #TA0471; conducted by [redacted] report dated 11/98; GLP)

A) Methods

[redacted]

B) Results

In vivo, effects at both volumes included increases in pulmonary arterial pressure (SS at 5 minutes; max 2X; Fig. and Table III.1), diastolic arterial pressure (significant for 20 minutes at 10 ml/kg; Table III.2), and heart rate (significant for 15 minutes). These effects appeared to be partly

volume dependent, with greater effects at the higher volume. Vomiting was seen in 4 out of 5 animals with both volumes. Plasma concentrations (parent) one hour post-dosing were 508 ± 58 and 478 ± 66 ug/ml after the 45 and 180 mg/ml solutions, respectively.

In vitro, the drug produced an increase in plasma and blood viscosities as well as a decrease in erythrocyte deformability (these were also seen in human blood at high concentrations in vitro). The no-effect concentration was 7.2 mg/ml and the effect was SS at 72 and 144 mg/ml (Tables III.3 and III.4).

C) Conclusions

The results indicate that an iv dose of 450 mg/kg infused over 5 min induces a transient increase in pulmonary arterial pressure (SS at 5 minutes), which was thought to be related to the increase in plasma and blood viscosities and decrease in erythrocyte deformability seen in vitro, as well as an increase in heart rate and diastolic arterial pressure (SS for 15 to 20 minutes), that was thought to be related to the emetic effects induced in conscious dogs (not seen in previous study in anesthetized dogs). The effects on pulmonary arterial pressure, heart rate, and diastolic pressure also appeared to be partly related to the injection volume, however, with the effects being somewhat greater at the higher of the two volumes studied.

Table III.1

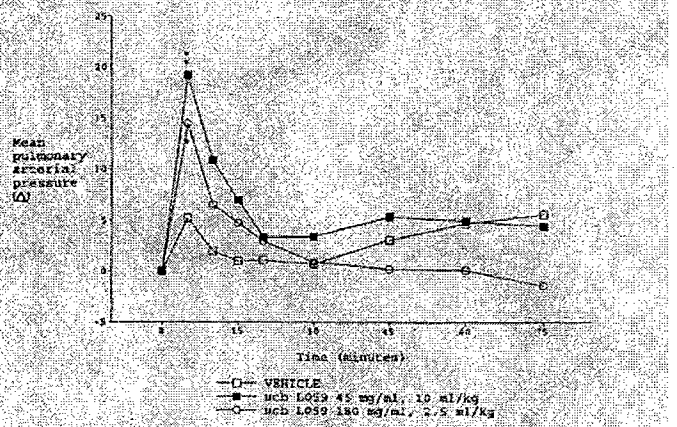
EFFECT OF ucb L059 ON MEAN PULMONARY ARTERIAL PRESSURE FOLLOWING INTRAVENOUS ADMINISTRATION IN THE CONSCIOUS DOG

TREATMENT		Predose values (mm Hg)	t=5 (Δ)	t=10 (Δ)	t=15 (Δ)	t=20 (Δ)	t=30 (Δ)	t=45 (Δ)	t=60 (Δ)	t=75 (Δ)	Emax (Δ)	Tmax (min)
VEHICLE	Mean	20.4	5.2	1.3	0.9	1.1	0.7	3.1	4.6	5.5	-5.5	t=75
10 ml/kg	SEM	2.7	1.2	1.1	1.4	1.7	2.1	1.1	4.7	4.9		
	N	5	5	5	5	5	5	5	5	5		
ucb L059	Mean	19.5	19.2	10.8	5.9	3.9	3.4	5.3	4.9	4.1	+19.2	t=5
45 mg/ml	SEM	1.8	9.1	4.7	3.8	2.5	2.4	2.9	3.3	3.5		
10 ml/kg	N	5	5	5	5	5	5	5	5	5		
	P	NS	**	NS	NS	NS	NS	NS	NS	NS		
ucb L059	Mean	20.2	14.5	6.5	4.7	2.9	0.9	0.2	0.1	-1.4	+14.5	t=5
180 mg/ml	SEM	1.6	4.3	1.9	1.4	1.6	1.4	0.4	1.2	1.7		
2.5 ml/kg	N	5	5	5	5	5	5	5	5	5		
	P	NS	*	NS	NS	NS	NS	NS	NS	NS		

Predose values: mean pulmonary arterial pressure measured before the administration expressed in mm Hg.
t=5 to t=75: variation calculated by substraction of predose values.
t: time in minutes following dosing.
Vehicle: 0.9% isotonic solution of sodium chloride.
Emax: maximal effect expressed as variation calculated in relation to predose values.
Tmax: time in minutes corresponding to the maximal effect (Emax).
Mean: mean value.
SEM: Standard Error of the Mean.
N: number of animals.
Predose values: NS: $P > 0.05$, when compared with the control group dosed with the vehicle: analysis of variance.
t=5 to t=75: NS: $P > 0.05$, *: $P \leq 0.05$, **: $P \leq 0.01$, when compared with the control group dosed with the vehicle: analysis of variance for repeated measurements with NEWMAN-KEULS test if $P \leq 0.05$.

Figure III.1

EFFECT OF ucb L059 ON MEAN PULMONARY ARTERIAL PRESSURE FOLLOWING INTRAVENOUS ADMINISTRATION IN THE CONSCIOUS DOG



Δ: variation calculated by substraction of predose values (t=0), in mm Hg
Vehicle: 0.9% isotonic solution of sodium chloride.
*: $P \leq 0.05$, **: $P \leq 0.01$, when compared with the control group dosed with the vehicle: analysis of variance for repeated measurements with NEWMAN-KEULS test if $P \leq 0.05$

Table III.2

EFFECT OF ucb L059 ON DIASTOLIC ARTERIAL PRESSURE FOLLOWING INTRAVENOUS ADMINISTRATION IN THE CONSCIOUS DOG

TREATMENT		Predose values (mm Hg)	t=5 (Δ)	t=10 (Δ)	t=15 (Δ)	t=20 (Δ)	t=30 (Δ)	t=45 (Δ)	t=60 (Δ)	t=75 (Δ)	Emax (Δ)	Tmax (min)
VEHICLE 10 ml/kg	Mean	95	97	93	91	93	90	91	91	90	-4	t=45
	SEM	0	3	2	3	3	3	3	3	2		
	N	5	5	5	5	5	5	5	5	5		
ucb L059 45 mg/mL 10 ml/kg	Mean	97	94	90	75	76	88	94	93	93	+24	t=5
	SEM	1	5	7	6	6	4	4	3	3		
	N	5	5	5	5	5	5	5	5	5		
	P		**	**	**	**	NS	NS	NS	NS		
ucb L059 180 mg/mL 2.5 ml/kg	Mean	97	95	90	84	88	95	96	91	92	+10	t=10
	SEM	1	2	4	4	2	5	2	2	2		
	N	5	5	5	5	5	5	5	5	5		
	P	NS	NS	*	NS	NS	NS	NS	NS	NS		

Predose values: diastolic arterial pressure measured before the administration expressed in mm Hg.
t=5 to t=75: variation calculated by substraction of predose values.
t: time in minutes following dosing.
Vehicle: 0.9% isotonic solution of sodium chloride.
Emax: maximal effect expressed as variation calculated in relation to predose values.
Tmax: time in minutes corresponding to the maximal effect (Emax).
Mean: mean value.
SEM: Standard Error of the Mean.
N: number of animals.
Predose values: NS: $P > 0.05$, ** $P \leq 0.01$, when compared with the control group dosed with the vehicle: analysis of variance with NEWMAN-KEULS test if $P \leq 0.05$.
t=5 to t=75: NS: $P > 0.05$, *: $P \leq 0.05$, **: $P \leq 0.01$, when compared with the control group dosed with the vehicle: analysis of variance for repeated measurements with NEWMAN-KEULS test if $P \leq 0.05$.

Table III.3

IN VITRO EFFECT OF ucb L059 SOLUTION
ON BLOOD VISCOSITY AT SHEAR SPEED OF 128.5 s^{-1}
WHEN ADDED IN A VOLUME OF 1 ml (360 mg/ml)
TO 4 ml OF BLOOD (ie 72 mg/ml)

TREATMENT		VEHICLE	ucb L059	Emax (Δ)
BLOOD VISCOSITY 128.5 s-1	Mean	3.59	4.61	+1.02
	SEM	0.03	0.05	
	N	5	5	
	P		***	
PLASMA VISCOSITY 128.5 s-1	Mean	1.07	1.59	+0.51
	SEM	0.02	0.14	
	N	5	5	
	P		*	
RELATIVE VISCOSITY 128.5 s-1	Mean	3.37	2.98	-0.38
	SEM	0.06	0.27	
	N	5	5	
	P		NS	

Blood, plasma and relative viscosities are expressed in mPa/s.
Vehicle: 0.9% isotonic solution of sodium chloride.
Emax: maximal effect expressed as variation calculated in relation to vehicle.
Mean: mean value.
SEM: Standard Error of the Mean.
N: number of animals.
NS: $P > 0.05$, *: $P \leq 0.05$, ***: $P \leq 0.001$, when compared with the control group dosed with the vehicle: Student's paired t test.

Table III.4

IN VITRO EFFECT OF ucb L059
ON ERYTHROCYTES DEFORMABILITY
WHEN ADDED IN A 1 ml VOLUME (360 mg/ml) TO
4 ml OF BLOOD (ie 72 mg/ml)

TREATMENT		VEHICLE	ucb L059	Emax (Δ)
TRANSIT TIME (ms)	Mean	1.21	1.72	+0.51
	SEM	0.07	0.14	
	N	5	5	
	P		*	
p25	Mean	0.85	0.91	+0.06
	SEM	0.03	0.04	
	N	5	5	
	P		*	
p50	Mean	0.97	1.05	+0.08
	SEM	0.06	0.05	
	N	5	5	
	P		*	
p75	Mean	1.12	1.23	+0.11
	SEM	0.05	0.05	
	N	5	5	
	P		*	
p90	Mean	1.32	1.76	+0.44
	SEM	0.07	0.18	
	N	5	5	
	P		NS	
p95	Mean	1.55	2.19	+0.65
	SEM	0.09	0.28	
	N	5	5	
	P		NS	
p99	Mean	2.31	5.20	+2.89
	SEM	0.16	0.80	
	N	5	5	
	P		*	

P25, 50, 75, 90, 95, 99: percentiles 25, 50, 75, 90, 95, 99 expressed in ms.
Vehicle: 0.9% isotonic solution of sodium chloride.
Emax: maximal effect expressed as variation calculated in relation to vehicle.
Mean: mean value.
SEM: Standard Error of the Mean.
N: number of animals.
NS: $P > 0.05$, *: $P \leq 0.05$, when compared with the control group dosed with the vehicle: Student's paired t test.

IV. Effects of ucb L059 on blood pressure, heart rate, pulmonary arterial pressure and electrocardiogram following single intravenous infusion in conscious dogs (RRLE02C1204; UCB study PSM0840; conducted by [redacted], report dated 1/03; GLP)

A) Methods

[redacted]

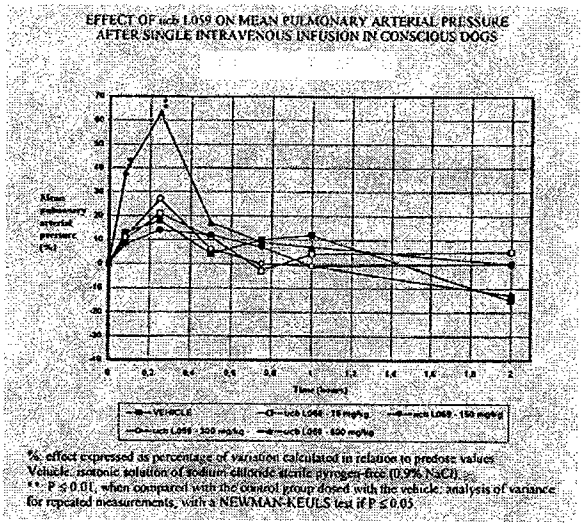
B) Results

During iv infusion of the vehicle, a short lasting increase in heart rate, femoral blood pressure (1 h) and pulmonary arterial pressure (30 min) was observed, associated with shortening of PR, PQ, and QT durations. The increase in femoral blood pressure, particularly systolic pressure, was less marked during drug infusion, with no dose-relationship. Retching was noted in 2/6 dogs at 300 mg/kg and vomiting was observed in 6/6 dogs at 600 mg/kg, primarily during the infusion. In parallel, at these two doses, heart rate increased (SS compared C). PR duration was shortened for up to 4 h at 600 mg/kg. Pulmonary artery pressure increased only during infusion of 600 mg/kg (up to 63% above predose values at 15 min) and returned to the predose range over the next 15 minutes (Fig and Table IV.1).

C) Conclusions

IV infusion of levetiracetam over 15 min (5 ml/kg) produced retching and vomiting and increased HR at doses ≥ 300 mg/kg, and transiently increased pulmonary arterial pressure (up to 60% above baseline) and shortened PR duration at a dose of 600 mg/kg. Plasma drug levels were not determined. In a 4-week dog toxicity study (below), concentrations at the end of a 15 min infusion were 136, 267, and 574 ug/ml at doses of 75, 150, and 300 mg/kg, respectively. Thus, the peak concentration at the no-effect level for increasing pulmonary arterial pressure was about 10-fold the Cmax in humans at the end of a single 15-min infusion of 1500 mg [redacted] administered in 100 ml).

Figure IV.1



% effect expressed as percentage of variation calculated in relation to predose values
Vehicle: isotonic solution of sodium chloride sterile pyrogen-free (0.9% NaCl).
** $P \leq 0.01$, when compared with the control group dosed with the vehicle; analysis of variance for repeated measurements, with a NEWMAN-KEULS test if $P \leq 0.05$

Table IV.1

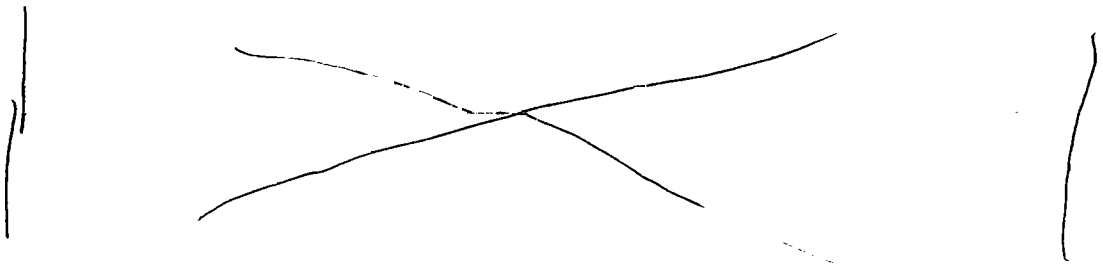
EFFECT OF ucb L059 ON MEAN PULMONARY ARTERIAL PRESSURE
AFTER SINGLE INTRAVENOUS INFUSION IN CONSCIOUS DOGS
MEAN DATA - % CHANGE OF BASELINE

TREATMENT		Baseline values (mHg)	t=0.08 (h)	t=0.25 (h)	t=0.5 (h)	t=0.75 (h)	t=1 (h)	t=2 (h)	t=3 (h)	t=4 (h)	t=6 (h)
VEHICLE	Mean	20	11	18	4	10	12	-15	-2	-2	10
	SEM	1	11	11	9	4	6	13	6	5	5
	N	6	6	6	6	6	5	6	6	6	6
ucb L059 75 mg/kg	Mean	22	16	21	11	-1	1	5	-21	-8	-11
	SEM	1	8	7	12	6	8	3	13	4	9
	N	6	6	6	6	6	6	6	6	6	6
	P	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
ucb L059 150 mg/kg	Mean	24	8	14	12	7	-1	-13	-8	-12	-8
	SEM	1	6	7	8	6	6	5	4	9	5
	N	6	6	6	6	6	6	6	6	6	6
	P	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
ucb L059 300 mg/kg	Mean	25	11	27	6	6	-1	0	-7	2	-3
	SEM	1	6	6	8	7	4	6	10	5	5
	N	6	6	6	6	6	6	6	6	6	6
	P	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
ucb L059 600 mg/kg	Mean	23	36	61	17	9	7	0	6	-2	0
	SEM	1	8	6	2	6	7	6	7	8	4
	N	6	6	6	6	6	6	6	6	6	6
	P	NS	**	**	NS	NS	NS	NS	NS	NS	NS

TREATMENT	t=8 (h)	t=12 (h)	t=16 (h)	t=20 (h)	t=24 (h)	Smax (%)	Tmax (h)
VEHICLE	9	6	16	12	4		
	3	2	5	5	5		
	6	6	6	6	6		
ucb L059 75 mg/kg	-4	-6	-1	-5	2	-21	t=6
	8	3	6	5	4		
	6	6	6	6	6		
	NS	NS	NS	NS	NS		
ucb L059 150 mg/kg	-7	-13	0	3	-7	-13	t=12
	5	8	3	4	4		
	6	6	6	6	6		
	NS	NS	NS	NS	NS		
ucb L059 300 mg/kg	-9	-11	-2	-4	-10	-22	t=16
	5	3	6	6	5		
	6	6	6	6	6		
	NS	NS	NS	NS	NS		
ucb L059 600 mg/kg	-1	-11	-5	-6	-8	+6	t=0.25
	4	7	4	5	4		
	6	6	6	6	6		
	NS	NS	NS	NS	NS		

V. Effect on cardiac action potentials in isolated canine Purkinje fibers (RRLE00E1601; UCB study TA0640; conducted by [redacted] report dated 7/00; GLP)

A) Methods



B) Results:

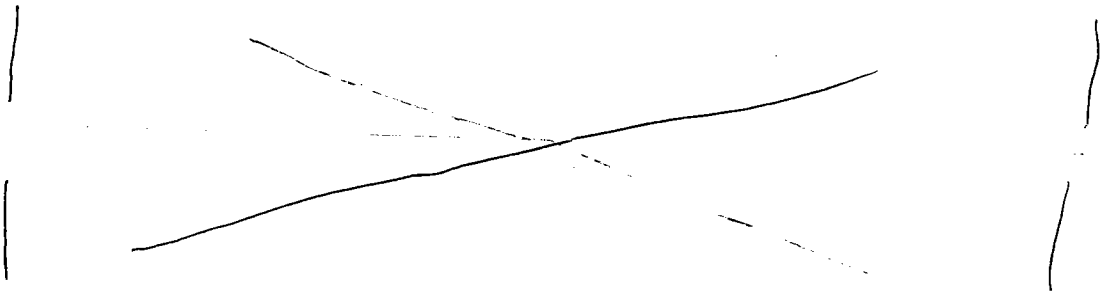
Concentrations of 100, 300 and 1000 ug/ml had no significant effects on any of the action potential parameters measured in Purkinje fibers paced at 1 and 0.5 Hz, and there was no significant difference between the vehicle and drug-treated preparations in steady state maximum rate of depolarization obtained by increasing the stimulation frequency from 1 to 3 Hz. The positive control, [redacted] induced statistically significant increases in APD_{60} and APD_{90} when administered to vehicle treated fibers (46% and 45%, respectively, at 1 Hz and 60% at 0.5 Hz. A prolongation of action potential duration that is inversely frequency dependent is consistent with the known activity of this compound.

C) Conclusions:

Levetiracetam concentrations of 100, 300 and 1000 ug/ml had no effect on any of the action potential parameters measured in isolated dog Purkinje fibers, indicating that QRS duration or QT interval should not be directly affected at equivalent concentrations.

VI. 4-Week 15-min (bid) intravenous toxicity study in rats (RRLE02B2202 Study Number: 867/063; UCB Study number: PSM0908; conducted by [redacted]; report dated 8/03; GLP)

A) Methods



B) Results

1. Observations

There were no deaths during the study. Immediately after dosing, muscular tonus was decreased in MD and HD animals.

2. Body Weights

A slight (NS) decrease in body weight gain was observed in HD males throughout the study. There were no treatment-related effects on food consumption.

3. Ophthalmology

There were not T-R effects.

3. Clinical Chemistry

a) Hematology

There were no T-R effects on hematology parameters.

b) Clinical Chemistry

There were no T-R effects on clinical chemistry parameters.

c) Urinalysis

During the last week of treatment, high water intake was observed in HD males. A dose-related increase of urine specific gravity was observed in all treated males and in HD females, and proteinuria was noted in HD males.

d) Plasma drug levels

Concentrations of parent and metabolite were somewhat higher in males than in females. Plasma levels of parent at the end of the infusion on Day 27 were 254, 659, and 2043 ug/ml in males and 226, 626, and 1700 ug/ml in females at the

LD, MD, and HD, respectively. Plasma levels of the major metabolite ucb L057 were 0.35, 0.85, and 3.1 ug/ml in males and 0.3, 0.75, and 1.9 ug/ml in females, respectively.

4. Necropsy

a) Organ Weights

Absolute and relative kidney weights were increased (SS) in HD males and absolute kidney weights were increased in MD males.

b) Gross Pathology

There were no findings considered T-R.

c) Microscopic Pathology

In the kidney, incidences and severity of hyaline droplets and basophilic tubules were greater than controls at all dose levels (dose related) in males (Table VI.1). Granular casts were seen in five HD males. These changes are characteristic of hyaline droplet nephropathy, which was also seen in rats with oral levetiracetam. In the liver, minimal centrilobular hypertrophy was seen in all males and 2/10 females at the HD and in 4/10 MD males. This was also seen in the oral toxicity studies. Incidences of injection site changes (venous/perivenous fibroplasia accompanied by intimal proliferation) were increased at all doses in both sexes (Table VI.2).

C) Conclusions

IV administration of levetiracetam (225, 630, or 1800 mg/kg/day) for 4 week produced effects on the liver (minimal centrilobular hypertrophy in MD and HD males and HD females) and kidney (increased weights in HD males, increased incidences and severity of hyaline droplets and basophilic tubules at all doses in males, granular casts in HD males), and injection site changes (venous/perivenous fibroplasia accompanied by intimal proliferation at all doses in both sexes). However, other than the injection site changes, there were no apparent new toxic effects associated with iv administration of levetiracetam for 4 weeks compared to oral administration.

Table VI.1

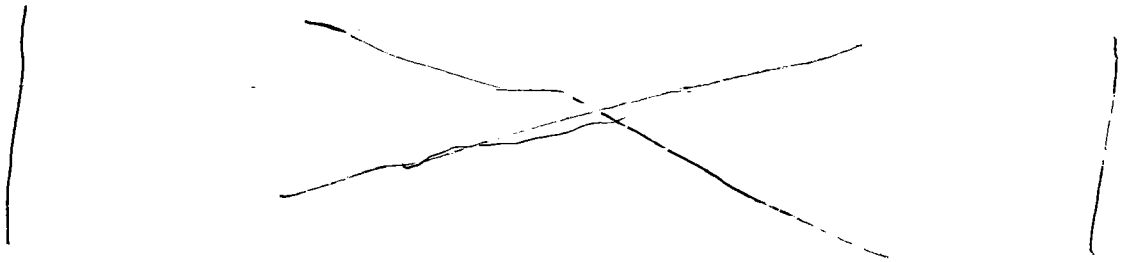
incidence of treatment-related changes in the kidneys								
Sex	Male				Female			
Dosage level ucb L059 (mg/kg/day)	0	225	630	1800	0	225	630	1800
Number examined	10	10	10	10	10	10	10	10
Basophilic tubules, focal								
Minimal	4	8	9	6	0	1	3	0
Slight	0	0	1	3	0	0	0	0
Moderate	0	0	0	1	0	0	0	0
Total	4	8	10	10	0	1	3	0
Casts, granular, medulla								
Minimal	0	0	1	3	0	0	0	0
Slight	0	0	0	1	0	0	0	0
Moderate	0	0	0	1	0	0	0	0
Total	0	0	1	5	0	0	0	0
Hyaline droplets, proximal tubules, prominent								
Minimal	2	3	2	0	0	0	0	0
Slight	0	1	7	8	0	0	0	0
Moderate	0	0	0	2	0	0	0	0
Total	2	4	9	10	0	0	0	0

Table VI.2

incidence of treatment-related changes at the injection sites								
Sex	Male				Female			
Dosage level ucb L059 (mg/kg/day)	0	225	630	1800	0	225	630	1800
Number examined	10	10	10	10	10	10	10	10
Injection site 1: fibroplasia, venous/perivenous								
Minimal	0	0	1	3	2	0	3	4
Slight	0	0	0	2	0	0	0	1
Total	0	0	1	5	2	0	3	5
Injection site 2: fibroplasia, venous/perivenous								
Minimal	0	0	0	0	0	0	1	4
Slight	0	0	0	7	0	0	0	1
Total	0	0	0	7	0	0	1	5
Injection site 2: intimal proliferation								
Minimal	0	0	2	3	2	4	3	5
Slight	0	1	0	0	0	1	1	1
Total	0	1	2	3	2	5	4	6

VII. 4-Week 15-min (bid) intravenous toxicity study in dog (RRLE02B2202 Study Number: 867/063; UCB Study number: PSM0908; conducted by , report dated 8/03; GLP)

A) Methods



B) Results

1. Observations

There was no mortality during the study. Salivation at the time of treatment was noted in treated groups with D-R severity.

2. Body Weights

There were no treatment-related effects on body weight or food consumption.

3. Ophthalmology

There were not T-R effects.

4. ECG

There were not T-R effects.

5. Clinical Chemistry

a) Hematology

Decreased RBC parameters were found in treated animals at all doses. The effect was not clearly D-R and values remained within the historical control range in all but one case; however, the lowest values were in the HD group, where 1 male had an RBC count (4.99 vs control mean of 6.53 x 1000/mm^3) that was below the historical control range and this was found to correlate with a decrease in the bone marrow smear erythroid series at the HD (decreased M/E ratio). This was considered a T-R effect at this dose.

b) Clinical Chemistry

A slight increase in chloride concentration was observed in some MD and HD females (4 and 7% compared to pretest). This change was not considered of toxicological relevance. There were no other T-R effects on clinical chemistry parameters.

c) Urinalysis

There were no T-R effects.

d) Plasma drug levels

Concentrations of parent and major metabolite were similar in males and females. Plasma levels of parent drug were 136, 267, and 574 ug/ml at the end of the infusion on Day 0 and 145, 277, and 550 ug/ml at the end of the infusion on Day 23 at the LD, MD, and HD, respectively. Plasma levels of ucb L057 were 1.66, 2.89, and 4.79 ug/ml and 2.0, 3.48, and 5.52 ug/ml, respectively. AUCs for parent drug were 944, 1886, and 3959 ug.h/ml on Day 0 and 952, 1732, and 3272 ug/ml on Day 23 at the LD, MD, and HD, respectively. AUCs for ucb L057 were 24.7, 41.9, and 72.6 and 28.2, 44.8, and 71.4 ug.h/ml, respectively.

4. Necropsy

a) Organ Weights

No T-R findings.

b) Gross Pathology

There were no findings considered T-R.

c) Microscopic Pathology

Histopathological examination showed no evidence of T-R effects.

C) Conclusions

Effects seen after iv administration of doses of 75, 150, and 300 mg/kg bid for 4 weeks included salivation during dosing, a slight increase in plasma chloride concentration in MD and HD females, decreased RBC parameters, and a decreased erythroid series in bone marrow. There were no apparent new toxic effects associated with iv administration of levetiracetam for 4 weeks compared to oral administration. Although there were some slight hematological and clinical chemistry effects, the no adverse effect level (NOAEL) was considered to be 300 mg/kg/day.

Summary and Evaluation

In acute iv (bolus) toxicity studies in mice, rats and dogs, levetiracetam produced primarily CNS-related clinical signs in rodents, including unsteady gait, proneness, ataxia, loss of righting, and decreased motor activity, while in dogs salivation, nervousness, agitation, and increased heart rate were the primary signs. These signs were similar to those seen after oral administration but of greater severity. Deaths (preceded by cyanosis, dyspnea, and, in mice, convulsions) were seen at the highest doses tested in rodents (maximum non-lethal iv dose in rats = 750 mg/kg vs >5000 po). No deaths were reported in dogs at single iv (bolus) doses of up to 1200 mg/kg. However, hemodynamic effects were seen in dogs following single iv infusion (5-15 min) of 50 - 600 mg/kg. In the first study in 4 anesthetized male dogs, cumulative doses of 0 (saline vehicle), 50, 150, and 450 mg/kg were infused over 5 min at a volume of 2.5 ml/kg. There was a dose-related increase in pulmonary artery pressure at all doses (up to 4-fold pre-dose value at HD; seen in 2/4, 4/4, and 4/4 dogs at the respective doses; **Table II.1**). The maximum effect was generally seen within 5 minutes of drug administration, with values returning to baseline over the next 15 minutes. Drug levels determined 45 minutes after administration were 57.8, 208 and 634 ug/ml, at the respective doses. The LD value, which would not be the Cmax, is similar to the human Cmax at the end of a single 15-min infusion of 1500 mg (~~~~ administered in 100 ml).

In a follow-up study in 5 male dogs, an iv dose of 450 mg/kg, either as a concentration of 45 mg/ml in a volume of 10 ml/kg or 180 mg/ml in a volume of 2.5 ml/kg, was infused over 5 min. Both volumes increased pulmonary arterial pressure (SS at 5 minutes; max 2X; **Fig and Table III.1**) as well as diastolic arterial pressure (significant for 20 minutes at 10 ml/kg) and heart rate (significant for 15 minutes). These effects appeared to be partly volume dependent, with the higher volume producing greater effects. Vomiting was seen in 4 out of 5 animals with both volumes of administration, and the increases in heart rate and diastolic arterial pressure (SS for 15 to 20 minutes) were thought to be related to the emetic effects since they were not seen in previous study in anesthetized dogs. Plasma concentrations (parent) one hour post-dosing in this dog study were 508 ± 58 and 478 ± 66 ug/ml after the 45 and 180 mg/ml solutions, respectively. In vitro in dog blood, the drug was shown to increase plasma and blood viscosities and decrease erythrocyte deformability at concentrations of 72 and 144 mg/ml (these effects were also seen in human blood at high concentrations [100 mg/ml] in vitro), with a no-effect concentration of 7.2 mg/ml. These in vitro findings were thought to "suggest a possible hemorheological change due to high local concentrations in the venous circulation, producing increased blood viscosity and decreased erythrocyte deformability, resulting in a transient rise in pulmonary artery pressure."

In a more recent iv cardiovascular study in dogs (3/sex), doses of 0 (saline vehicle), 75, 150, 300, and 600 mg/kg were infused over 15-minutes at a volume of 5 ml/kg (infusion rate of 20 ml/kg/h). Retching was seen in 2/6 dogs at 300 mg/kg and vomiting was observed in 6/6 HD dogs, primarily during the infusion. In parallel, at these two highest doses, heart rate increased (SS compared C). PR duration was shortened for up to 4 h at 600 mg/kg. Pulmonary artery pressure increased during infusion of 600 mg/kg (up to 63% above predose values) and returned to the predose range in the next 15 minutes (**Fig and Table IV.1**). The increase in HR was attributed to the emetic effect, while the increase in PAP was attributed to a distinct mechanism ("probably haemorrheological changes"). Plasma drug levels were not determined in this study, but in a 4-week toxicity study, concentrations at the end of a 15 min infusion were 136, 267, and 574 ug/ml at doses of 75, 150, and 300 mg/kg, respectively. Thus, the peak concentration at the no-effect level for increasing pulmonary arterial pressure was about 10-fold the Cmax in humans at the end of a single 15-min infusion of 1500 mg.

Repeat dose iv rat studies of up to 4 weeks duration were conducted. In the 4-week study, doses of 225, 630, or 1800 mg/kg/day (given as divided doses, 10 hr apart) were administered iv as a 15-minute infusion. There were no deaths. A treatment-related decrease in muscular tonus was noted at ≥630 mg/kg/day (315 mg/kg bid), with males being more affected than females (drug levels higher in males than in females). There were no treatment-related effects on body weights (slight, NS effect in males), food consumption, ophthalmology, hematology or clinical chemistry parameters. During the last week of treatment, increased water intake was seen in HD males. A dose-related increase in urine specific gravity was observed in all treated males and in HD females, and proteinuria was noted in HD males. Liver and

kidney weights were increased in males, and histopathological examination showed increased incidences of injection site changes (venous/perivenous fibroplasia accompanied by intimal proliferation) at all doses in both sexes, minimal centrilobular hypertrophy in MD and HD males and HD females, and increased incidences and severity of hyaline droplets and basophilic tubules at all doses in males, with granular casts in HD males. These later changes are characteristic of hyaline droplet nephropathy, which was also seen in rats with oral levetiracetam. At the NOAEL of 225 mg/kg/day, AUCs of parent drug were 1196 ug.h/ml in males and 910 ug.h/ml in females. AUCs of the major metabolite, ucb L057, were 15 ug.h/ml in males and 11.5 ug.h/ml in females, respectively. In humans, AUCs of 372 and 36 ug.h/ml were measured for parent and metabolite, respectively, after a 1500 mg bid iv dose. Based on the limited toxicity seen in this study, it appears that higher doses could have been evaluated. However, it can be considered an adequate bridging study, since exposures were similar to those produced in the oral toxicity studies, which would allow any toxicities unique to iv dosing to be identified within this exposure range. (Keppra injection is intended to be bioequivalent to the approved oral dosage forms in clinical use.)

Repeat dose iv dog studies of up to 4 weeks duration were conducted. In the 4-week study, doses of 150, 300 or 600 mg/kg/day (75, 150 or 300 mg/kg bid) were given as a 15-minute iv infusion. There were no deaths. Dose-related salivation at the time of treatment in all treated groups was the only clinical sign noted. There were no treatment-related effects on body weight, food consumption, ophthalmology, ECG parameters or urinary parameters. At the end of the treatment period, decreased RBC parameters were found in treated animals at all doses. The effect was not clearly D-R and values remained within the historical control range in all but one case, but the lowest values were in the HD group, where 1 male had an RBC count (4.99 vs control mean of 6.53 x 1000/mm^3) that was below the historical control range. This was found to correlate with a decrease in the bone marrow smear erythroid series at the HD (decreased M/E ratio). There were no treatment-related macroscopic or microscopic findings. The NOAEL in this study (150 mg/kg bid) was associated with AUCs of 1886 ug.h/ml for parent and 41.9 ug.h/ml for the major metabolite, ucb L057. In humans, AUCs of 372 and 36 ug.h/ml were measured for parent and metabolite, respectively, after a 1500 mg bid iv dose. While it appears that higher doses could have been evaluated in this study, the study can be considered an adequate bridging study in that exposures similar to those produced in the oral toxicity studies were achieved, so that any toxicities unique to iv dosing at equivalent exposures could have been identified.

For the most part, the effects seen in rats and dogs following iv administration for up to 4 weeks, in studies that are considered adequate to support this application, were similar to those already reported following oral administration (NDA 21-035 and 21-505). However, an effect on pulmonary arterial pressure (↑ PAP) in dogs had not been reported with oral dosing. An initial study in anesthetized dogs indicated that this effect could occur at a relatively low iv dose (50 mg/kg) when the drug was infused rapidly (5 min). A subsequent study in conscious dogs with a slower infusion rate (15 min) found the effect only at concentrations about 10X those measured in humans at a dose of 1500 mg. A clinical study at this dose given over 15 min did not detect any changes in PAP (see clinical review). However, it seems likely that this effect could occur at higher doses and/or more rapid rates of infusion. Depending on the clinical assessment of the seriousness of a transient elevation in PAP, some statement in labeling about the potential for such effects may be warranted. While the oral juvenile animal (rat and dog) studies are considered adequate for assessing most toxicity, given the complete absorption of levetiracetam after oral administration (>90% bioavailability in all species), hemodynamic effects and other possible effects unique to iv dosing were not evaluated in young animals, so there is no preclinical information to directly address the potential for such effects

Recommendations

The NDA is approvable with respect to the pharmacology/toxicology portion. Recommendations concerning the proposed labeling are made below.

cc:
NDA (21-872)
Div File
HFD-120/EFisher/LFreed/CCalder

J.E. Fisher, Ph.D.

Labeling

Mechanism of Action

The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown. The antiepileptic activity of levetiracetam was assessed in a number of animal models of epileptic seizures. Levetiracetam did not inhibit single seizures induced by maximal stimulation with electrical current or different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization. Levetiracetam also displayed inhibitory properties in the kindling model in rats, another model of human complex partial seizures, both during kindling development and in the fully kindled state. The predictive value of these animal models for specific types of human epilepsy is uncertain.

In vitro and *in vivo* recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity.

Levetiracetam at concentrations of up to 10 μM did not demonstrate binding affinity for a variety of known receptors, such as those associated with benzodiazepines, GABA (gamma-aminobutyric acid), glycine, NMDA (N-methyl-D-aspartate), re-uptake sites, and second messenger systems. Furthermore, *in vitro* studies have failed to find an effect of levetiracetam on neuronal voltage-gated sodium or T-type calcium currents and levetiracetam does not appear to directly facilitate GABAergic neurotransmission. However, *in vitro* studies have demonstrated that levetiracetam opposes the activity of negative modulators of GABA- and glycine-gated currents and partially inhibits N-type calcium currents in neuronal cells.

A saturable and stereoselective neuronal binding site in rat brain tissue has been described for levetiracetam. Experimental data indicate that this binding site is the synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle exocytosis. Although the molecular significance of levetiracetam binding to synaptic vesicle protein SV2A is not understood, levetiracetam and related analogs showed a rank order of affinity for SV2A which correlated with the potency of their antiseizure activity in audiogenic seizure-prone mice. These findings suggest that the interaction of levetiracetam with the SV2A protein may contribute to the antiepileptic mechanism of action of the drug.

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/s/

Edward Fisher
1/20/2006 04:02:20 PM
PHARMACOLOGIST

Lois Freed
1/20/2006 05:11:17 PM
PHARMACOLOGIST
I concur; however, I would recommend further communication with the sponsor regarding the PAP findings in dog.