# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-285**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Clinical Pharmacology/Biopharmaceutics Review

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|---|---|
| PRODUCT (Generic Name): | Levetiracetam |
| PRODUCT (Brand Name): | KEPPRA XR |
| NDA: | 22-285 |
| DOSAGE FORM: | Extended release tablet |
| DOSAGE STRENGTHS: | 500 mg. |
| INDICATION: | Adjunctive therapy, Partial Onset Seizures |
| NDA TYPE: | 3S |
| SUBMISSION DATES: | 11/29/2007 |
| SPONSOR: | UCB, Inc. |
| REVIEWER: | Gilbert J. Burckart, Pharm.D. |
| TEAM LEADER: | Ramana Uppoor, Ph.D. |
| OCPB DIVISION: | DCP I, HFD 860 |
| OND DIVISION: | HFD 120, DNP |

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## *1. Executive Summary*

Levetiracetam (Keppra® or (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide) is an anticonvulsant with a unique mechanism of action.

This application NDA 22-285 is for a new solid oral dosage form with extended release characteristics intended for once-a-day administration for the adjunctive treatment of partial onset seizures. The sponsor has applied for use in patients — years of age. b(4)

Keppra® was originally approved in 1999 (NDA 21-035) in multiple strength immediate release tablets (250, 500 and 750 mg) for the adjunctive treatment of partial onset seizures in adults. Additional FDA approvals have included:

- Oral solution (NDA 21-505) for the same indication, approved in 2003
- Children ≥ 4 year old for the same indication in 2005
- 1000 mg tablets approved in 2006
- Injecton (100 mg/ml) in 2006
- Approval for adjunctive therapy in myoclonic seizures in 2006
- Approval for treatment of generalized clonic-tonic seizures in 2007

The extended release dosage form (Keppra XR) considered in this application is a 500 mg. tablet. The development program for this extended release dosage form has consisted of 5 studies with Keppra XR, four of which are in healthy subjects and one of which was in patients. One additional group analysis and simulation was also conducted. The first study was N01173, and examined the absorption of levetiracetam from various portions of the gut to see if an extended release product was feasible. The second study was N01140, which tested three formulations of extended release tablets in 12 healthy subjects. The third study (N01160) was a pivotal randomized three way crossover study in 24 healthy subjects of Keppra immediate release 500 mg tablets versus Keppra XR 1000 mg (two 500 mg tablets) administered as a single dose and as multiple doses while fasting, along with a study after a meal. The fourth study was a dose proportionality study of doses of Keppra XR 1000, 2000 and 3000 mg in 24 healthy volunteers. The fifth study was a double blind, randomized placebo-controlled study of 1000 mg/day in 158 seizure patients of 12-70 years old examining efficacy and safety. In this clinical study, 77 patients were exposed to Keppra XR over a twelve week period and had trough plasma concentrations of levetiracetam measured.

The primary issues identified in the review were: (i) the small number of 12-16 year old pediatric patients and their trough levels in the clinical study, (ii) the lack of definitive dosing information in geriatric patients in the

analysis, and (iii) the identification of significantly different trough concentrations in the Hispanic patients in comparison to the Caucasian patients.

These issues have been discussed from the Clinical Pharmacology **perspective in the 'Summary of Findings' and the 'Question Based Review' sections of the Review.**

### *1.1. Recommendations*

The Office of Clinical Pharmacology/Division of Clinical Pharmacology I (OCP/DCP-1) has reviewed NDA #22-285.

OCP finds this application acceptable provided that labeling recommendations by the Agency on pages 38-62 of the review are accepted by the sponsor and the sponsor agrees to the phase 4 commitment below, and with the following exceptions:

(i) That Keppra XR be approved for use only in adults age 16 years and older; and
(ii) That Keppra XR not be recommended for use in patients with end stage renal disease on dialysis.

Please forward the labeling recommendations, phase 4 commitment and the comment provided below to the sponsor.

### *1.2. Identify recommended Phase 4 study commitments if the NDA is judged approvable*

Insufficient pharmacokinetic and pharmacodynamic studies have been performed with this product to make appropriate dosing recommendations and gather safety information for the geriatric population, who were essentially not studied with Keppra XR (one patient). *Therefore a pharmacokinetic study should be performed in geriatric patients with Keppra XR to provide specific dosing information.*

***1.25 Comment to the sponsor:***
Hispanic patients had significantly higher (40%) trough concentrations in study N01235 than did Caucasian patients with Keppra XR. Please evaluate all the available data (PK and safety) for Levetiracetam to understand any differential PK or safety of levetiracetam in Hispanic patients, [redacted] b(4)

### *1.3 Summary of Clinical Pharmacology Findings*

The biopharmaceutical properties of levetiracetam are advantageous for creating an extended release dosage form. The drug has little or no interaction with cytochrome P450 enzymes and membrane transporters, is absorbed throughout the gut, as was demonstrated in study N01173, and the absorption of the drug is minimally affected by food. Since the drug has been in use since 1999, clinical studies had demonstrated dose-proportional plasma levels with doses in adults exceeding 3000 mg, so it was not surprising that the sponsor was able to demonstrate dose proportionality with Keppra XR at 1000, 2000, and 3000 mg in healthy subjects (N01260). An in vitro study of dose dumping with alcohol demonstrated no significant affect with 40% ethanol versus control. The pivotal food and fasting 3-way crossover study in healthy subjects (N01160) demonstrated comparable Cmax and AUC (with lower Cmin) of the Keppra XR compared to the Keppra immediate release tablets. Each of these studies are reviewed in the question-based review below.

The clinical study (N01235) was both informative in what it included, and in what information it could not provide. [redacted] b(4)
, only seven adolescent subjects aged 12-16 actually received Keppra XR in the clinical study. Mean trough concentrations for patients having at least two levels on the 1000 mg/day dosage was 77% higher in 6 adolescent subjects than in the adults. Keppra XR comes only as a 500 mg tablet, so does not have the flexibility for dosing in pediatric patients that would be available for Keppra immediate release tablets (250, 500, 750, 1000 mg) and oral liquid.

Another patient group which had divergent plasma levetiracetam trough concentrations were the Hispanic patients, who had 40% higher trough concentrations than did the Caucasian patients.

Patient populations which were not studied included geriatric patients, since only one elderly patient received Keppra XR, and patients with renal impairment. Since the drug is primarily excreted unchanged in the urine, changes in renal function affect both of these groups of patients.

In conclusion, Keppra XR demonstrates the characteristics of an extended release dosage form which shows similar exposure in once daily dosing to the immediate release dosage form given twice daily in healthy subjects. The clinical study was in a relatively small patient population, and raised questions regarding Keppra XR's use in pediatric patients and in elderly patients.

Signature Page:

Gilbert J. Burckart, Pharm.D.
Clinical Pharmacology Reviewer
Office of Clinical Pharmacology

Ramana Uppoor, Ph.D.
Clinical Pharmacology Team Leader
Office of Clinical Pharmacology

Mehul Mehta, Ph.D.
Director, Division 1
Office of Clinical Pharmacology

## *2. Question-Based Review (QBR)*

### *2.1. General attributes of the drug*

Levetiracetam (ucb L059) is a pyrrolidone derivative and is chemically designated (S)-α-ethyl-2-oxo-1-pyrrolidone acetamide with a molecular weight of 170.21 and molecular formula of C8H14N2O2. Recent studies have shown that the antiepileptic effect of levetiracetam is linked to a novel mechanism of action, based on the binding of the drug to the synaptic vesicle protein SV2A. The extent to which this binding contributes to the levetiracetam mode of action remains be elucidated.

**What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?**

KEPPRA® (levetiracetam) 250 mg, 500 mg and 750 mg tablets were approved as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy (NDA 21-035) on 30 November 1999. KEPPRA (levetiracetam) oral solution (100 mg/mL) is a grape-flavored liquid approved for the same indication on 15 July 2003 (NDA 21-505). KEPPRA tablets and oral solution were approved as adjunctive therapy in the treatment of partial onset seizures in children 4 years of age and older with epilepsy on 21 June 2005. KEPPRA 1000 mg tablet was approved on 06 January 2006. KEPPRA (levetiracetam) injection 500 mg/5 mL (100 mg/mL) was approved as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy (NDA 21-872) on 31 July 2006. KEPPRA tablets and oral solution were approved as adjunctive therapy in the treatment of myoclonic seizures in patients 12 years and older with juvenile myoclonic epilepsy on 15 August 2006. KEPPRA tablets and oral solution were approved as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients 6 years and older with idiopathic generalized epilepsy on 19 March 2007. KEPPRA injection was approved as adjunctive therapy in the treatment of myoclonic seizures in adults with juvenile myoclonic epilepsy on 12 September 2007. A supplement to add the indication of adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults with idiopathic generalized epilepsy for KEPPRA injection is currently under review.

Table 2:1 Major U.S. Approvals of KEPPRA

| NDA / sNDA | Indication | Patient Population | Formulation | Approval Year |
|---|---|---|---|---|
| 21-035 | Partial Onset Seizures | ≥16 years old | IR Tablet | 1999 |
| 21-505 | Partial Onset Seizures | ≥16 years old | Oral Solution | 2003 |
| 21-035 / S-040<br>21-505 / S-007 | Partial Onset Seizures | ≥ 4 years old | IR Tablet and Oral Solution | 2005 |
| 21-872 | Partial Onset Seizures | ≥16 years old | I.V. Injection | 2006 |
| 21-035 / S-050<br>21-505 / S-009 | Myoclonic Seizures | ≥ 12 years old | IR Tablet and Oral Solution | 2006 |
| 21-035 / S-057<br>21-505 / S-013 | Primary Generalized Tonic Clonic (PGTC) Seizures | ≥ 6 years old | IR Tablet and Oral Solution | 2007 |
| 21-872 / S-003 | Myoclonic Seizures | ≥ 16 years old | I.V. Injection | 2007 |
| 21-872 / S-005 | Primary Generalized Tonic Clonic (PGTC) Seizures | ≥ 16 years old | I.V. Injection | Pending |

### 2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Keppra XR will be supplied for oral administration as an oblong, white filmcoated extended release tablet with red imprinting, containing 500 mg of levetiracetam. The tablets will be supplied in bottles [redacted] he quantitative composition of levetiracetam extended release tablets, 500 mg is provided in Table 3:1. b(4)

Table 3:1 Proposed Composition for Levetiracetam Extended Release Tablets, 500 mg

| Ingredient | Amount per Tablet (mg) | Function | Reference to Standard |
|---|---|---|---|
| Levetiracetam | 500.00 | Active ingredient | UCB Specification |
| Hypromellose | [redacted] | | Ph. Eur. |
| Colloidal anhydrous silica | | | Ph. Eur. |
| Polyethylene glycol, 6000 | | | Ph. Eur. |
| Magnesium Stearate | | | Ph. Eur. |
| [redacted] | | | UCB Specification |
| | | | UCB Specification |

b(4)

***Dosage Form/Strengths:*** Keppra XR is an extended release tablet to be marketed only as a 500 mg. tablet. KEPPRA XR tablets are white, oblong-shaped, film-coated extended-release tablets imprinted in red with **"UCB 500XR" on one side and contain 500 mg levetiracetam.**

***Indication:*** Keppra XR is an antiepileptic drug indicated for adjunct therapy in the treatment of partial onset seizures in patients with epilepsy. b(4)

***Dosage and administration (Sponsor's Proposed):***
Treatment should be initiated with a dose of 1000 mg once daily. The daily dosage may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg

***Pharmacologic Class: Anticonvulsant, unique mechanism of action***

***Chemical Name***: (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide

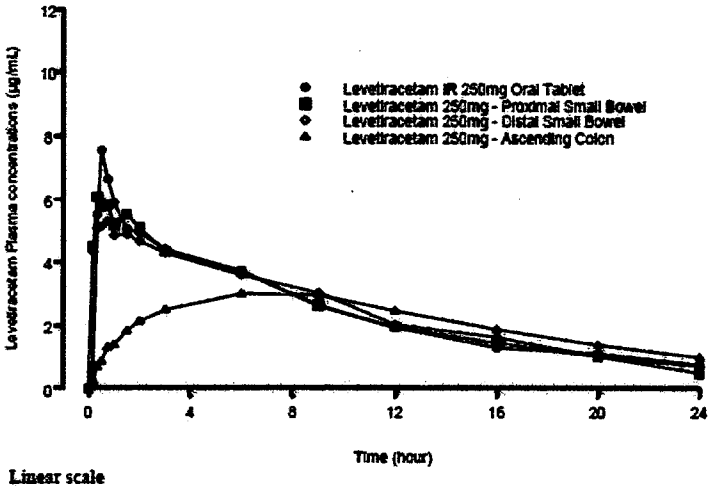
***Physical Characteristics:*** It is very soluble in water (104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane. (Solubility limits are expressed as g/100 mL solvent.)

***Site of absorption:***

The primary objective of this study (NO1173) was to determine the regional absorption profile of levetiracetam 250 mg from three different regions of the gastrointestinal tract (proximal small bowel, distal small **bowel, and ascending colon) using the** [redacted] **drug delivery** system compared with the 250 mg IR oral tablet absorption profile. b(4)

Nine male subjects were randomized and composed the ITT (intent to treat) population. Three subjects did not complete the study and were thus excluded from the PP (per protocol) population. One subject was excluded because in one period the capsule was not activated due to rapid transit, and two subjects were excluded due to discontinuation before the end of the four periods of treatment (only 6 completers were required per protocol). Mean plots for all regimen are shown in Figure 2:1 on the linear scale.

**Figure 2:1** **Mean Plasma Concentration vs. Time Profiles of Levetiracetam IR 250 mg Oral Tablet and Levetiracetam 250 mg Delivered to the Proximal Small Bowel, to the Distal Small Bowel and to the Ascending Colon via the [redacted] - N01173 PP Population** b(4)




Linear scale

Kinetic parameters for the 3 sites of absorption were:

**Table 2:5** **Summary of Levetiracetam Pharmacokinetic Parameters – N01173 PP Population**

| Dose and Route of Administration | Statistic[a] | Summary Pharmacokinetic Parameters (n=6) | | | | |
|---|---|---|---|---|---|---|
| | | $C_{max}$ (µg/mL) | $t_{max}$ (h) | AUC(0-t) (µg*h/mL) | AUC (µg*h/mL) | $t_{1/2}$ (h) |
| IR 250 mg Oral Tablet | Geometric mean | 8.44 | 0.500 | 58.96 | 66.64[b] | 7.64[b] |
| | Range | 6.15-10.5 | 0.333-0.750 | 53.2-65.8 | 61.2-72.2 | 6.82-8.30 |
| 250 mg Proximal Small Bowel | Geometric mean | 6.77 | 0.350 | 58.22 | 66.55 | 7.73 |
| | Range | 5.79- 8.55 | 0.163-1.50 | 53.2-67.2 | 60.0-79.8 | 6.72-8.86 |
| 250 mg Distal Small Bowel | Geometric mean | 6.69 | 0.668 | 59.63 | 67.82 | 7.63 |
| | Range | 3.68-9.68 | 0.163-3.00 | 53.1-68.3 | 60.3-76.4 | 5.75-9.21 |
| 250 mg Ascending Colon | Geometric mean | 3.37 | 7.497 | 51.49 | 59.91[c] | 7.49[c] |
| | Range | 2.70-3.97 | 2.17-9.00 | 45.5-61.4 | 54.1-63.2 | 7.08-7.91 |

[a] for $t_{max}$ median is reported instead of geometric mean.
[b] n = 5.
[c] n = 3.

Extent of absorption was similar following direct administration into proximal small bowel, distal small bowel and the IR tablet, as evidenced by comparable AUC values. Cmax was decreased, on average, by about 20% following administration into the proximal and small bowel compared to the IR tablet, while tmax values were, on average, comparable.

After direct administration into the ascending colon, the rate of levetiracetam absorption was lower and slower than that for the IR tablet given orally, as evidenced by an average decrease of about 60% in Cmax

and a corresponding increase in tmax of 7 hr, on average. Since for half of the subjects dosed it was not possible to appropriately characterize the terminal elimination phase, the extent of absorption was measured by the AUC(0-t). The extent of absorption from the ascending colon was comparable to that for the IR tablet.

Compared with the IR tablet, 95% confidence intervals of median difference of tmax values did encompass zero for proximal (-0.34; 0.75 h) and distal (-0.33 ; 2.25 h) small bowel. Comparative bioavailability based on AUC (proximal and distal small bowel) or AUC(0-t) (ascending colon) ratios as compared with IR tablets, were found to be 98.51%, 100.79% and 87.14% in the proximal small bowel, distal small bowel and ascending colon, respectively.

On average, compared to the oral administration of the IR Tablet, levetiracetam peak plasma concentrations were reduced by about 20% when administered either in the proximal or distal small bowel, and by about 60%, when administered in the ascending colon. Time to peak concentration was comparable between the IR tablet, the proximal and distal small bowel, while it was significantly delayed following administration into the ascending colon.

Retrospective analysis of the scintigraphic data confirmed activations at the target locations (proximal small bowel, distal small bowel or ascending colon) on twenty-three out of twenty-five occasions for the intention to treat (ITT) population and eighteen out of eighteen occasions for the per protocol (PP) population. The formulation appeared to be well tolerated. There were no deaths or serious adverse events and no subject discontinued because of adverse events attributable to the study medication.

Therefore a sustained release formulation of LEV was possible because of the absorption throughout the gut, even given the somewhat reduced absorption in the colon.

***Test formulations:***

The sponsor has investigated three different test formulations before deciding on the current formulation in this application. Study N01140 was a single dose, open-label pilot study comparing the pharmacokinetics of 3 test formulations of LEV XR (500 mg oral dose) with the LEV IR reference formulation in 12 healthy male volunteers. The study also assessed the influence of food on one of the three test formulations. All XR formulations exhibited similar pharmacokinetic profiles which were, however, distinct from the IR formulation. As expected, the rate of exposure of the LEV XR formulations was lower than the IR formulation (Cmax reduced by 53%),

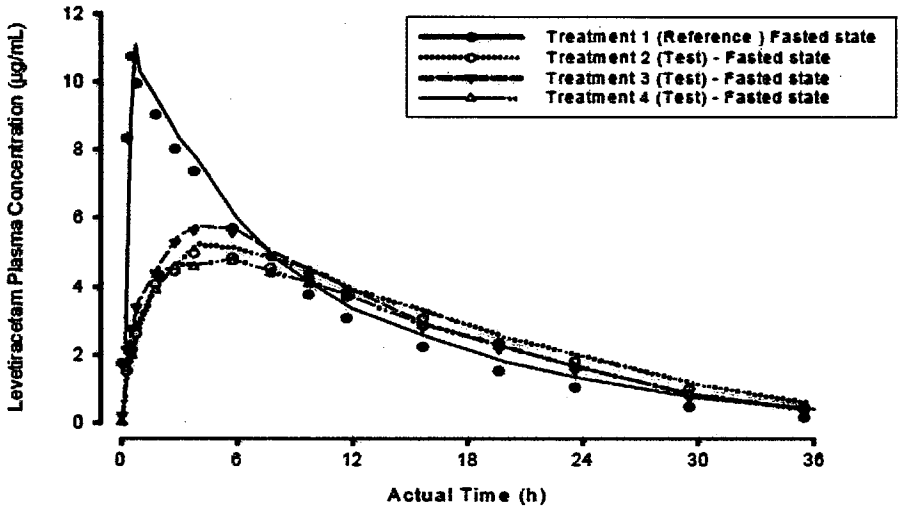
while extent of exposure remained equivalent between the different formulations. Considering Cmax and PTF (t=12h), geometric mean values were lower for the XR formulations than with the IR formulation. These results are consistent with the expected extended release properties of the test formulations.

Following food administration, pharmacokinetics of LEV XR administered as treatment 2 is slightly modified in terms of rate of absorption (Cmax increased and tmax delayed) while the extent of absorption remained equivalent (no change of AUC parameters). The three XR formulations showed equivalent pharmacokinetic properties. The extent of absorption was not modified by food intake, but an increase in Cmax and a delay of tmax of LEV XR were observed after food administration.

Geometric mean values of Cmax for XR formulations 2, 3 and 4 were reduced by 55%, 49% and 55% respectively compared to the IR formulation; tmax was delayed from 0.75 hours to 4 hours. The three LEV XR formulations exhibited an extent of exposure similar to that of the IR formulation. As compared to the reference treatment (112 and 117 µg.h/mL for AUC(0-t) and AUC), test treatments 2, 3 and 4 showed AUC(0-t) values of 106, 107,and 102 µg.h/mL, respectively, and AUC values of 115, 115, and 110 µg.h/mL, respectively. As expected, AUC(0-12) and PTF($\tau$=12h) of the three test treatments were reduced on average by 27% and 82%, respectively, and C12 was increased by 20% compared to the reference. Geometric mean values of Cav ($\tau$=12 h) ranged between 9.2 and 9.6 µg/mL for the test formulations and were very close to the reference (9.8 µg/mL). Relative bioavailability of levetiracetam using immediate release formulation as reference were identical between treatment 2, 3 and 4 with geometric mean values of 0.98, 0.98 and 0.94, respectively. Apparent terminal elimination half-life (t1/2), CL/F and Vz/F were similar between the LEV XR and IR formulations (on average 8.6 hours, 4.4 L/h and 55L versus 7.7 hours, 4.3 L/h and 47L, respectively). In the food effect assessment, Cmax value of levetiracetam was increased by 31% after food intake while time to peak concentration was delayed from 4 hours to 6 hours.

The following figure demonstrates the concentration time profile of the immediate release and three test formulations:

Figure 2:2 **Geometric Mean Plasma Concentration vs. Time Profiles of the 500 mg IR Formulation (Treatment 1) and the Three 500 mg XR Formulations (Treatments 2, 3 and 4) in Fasted Condition – N01140 PP Population (N = 12) (Top panel: linear scale; Bottom panel: semi-log scale)**




***Final formulation:***

Levetiracetam drug product will be supplied for oral administration as an oblong, white filmcoated extended release tablet with red imprinting, containing 500 mg of levetiracetam. The tablets will be supplied in bottles [redacted] b(4)

[redacted] The quantitative composition of levetiracetam extended release tablets, 500 mg is provided in Table 3:1.

Table 3:1 **Proposed Composition for Levetiracetam Extended Release Tablets, 500 mg**

| Ingredient | Amount per Tablet (mg) | Function | Reference to Standard |
|---|---|---|---|
| Levetiracetam | 500.00 | Active ingredient | UCB Specification |
| Hypromellose | [redacted] | | Ph. Eur. |
| Colloidal anhydrous silica | | | Ph. Eur. |
| Polyethylene glycol, 6000 | | | Ph. Eur. |
| Magnesium Stearate | | | Ph. Eur. |
| [redacted] | | | UCB Specification |
| | | | UCB Specification |

b(4)

### 2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

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.

Synaptic vesicles are the key organelles in neurotransmitter release from nerve cells. The specific function of the SV2 proteins and SV2A is largely unknown. In genetic knockout mice, reports demonstrate that SV2A knockout mice exhibit limited growth, and developed progressively severe seizures. Therefore SV2A may be an important regulator of synaptic function.

### 2.1.3. What are the proposed dosage(s) and route(s) of administration?

Total daily dose for LEV XR is recommended to be similar to that of the total daily dose recommendations for KEPPRA. The recommended dose range is 1000 to 3000 mg/day as once daily dosing. Treatment with LEV XR should be initiated with a daily dose of 1000 mg/day, given as once daily dosing. Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg.

## *2.2. General clinical pharmacology*

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In total, five studies have been conducted in the development of levetiracetam extended release tablet 500 mg (LEV XR). One efficacy and safety study (N01235) recruited patients ages 12 years of age and older with epilepsy, experiencing partial onset seizures. Three clinical pharmacology studies (N01140, N01160, and N01260) were conducted in healthy volunteers to investigate the bioavailability of the extended release tablet 500 mg as compared to the immediate release tablet 500 mg, the food effect, and the dose proportionality over the approved 1000 mg to 3000 mg dose range for immediate release KEPPRA. Data from these four studies includes a total of 137 unique subjects who have been exposed to levetiracetam extended release tablet 500 mg, including 79 patients with epilepsy and not including 79 patients exposed to placebo in the efficacy and safety study (N01235).

One retrospective population pharmacokinetic analysis (N01286) was also performed using the full dataset from the three studies that utilized the LEV XR tablets (N01160, N01260 and N01235). Levetiracetam plasma concentration-time data were modeled by non linear mixed effects modeling using NONMEM VI. The structural model was a one-compartment pharmacokinetic model, with first-order elimination and first-order absorption and lag-time.

The following table provides a brief overview of the studies:

**Table 2:2 Clinical Studies Included in NDA 22-285 for Levetiracetam Extended Release Tablet 500 mg**

| Study No. | No. Randomized (Exposed to XR) | Dates of Conduct / Countries | Overview of Design |
|---|---|---|---|
| N01235 | 158 (77) | 21-Aug-2006 – 30-May-2007 / Brazil, Finland, India, Mexico, Russian Federation, South Africa, Ukraine | Double-blind, placebo-controlled, randomized, 1000 mg once daily, as add-on therapy in patients 12 – 70 years of age with refractory epilepsy with POS; 8-week baseline followed by 12 weeks of treatment. |
| N01173 | 9 (0) | 03-Jun-2004 – 28-Jul-2004 / United Kingdom (UK) | Single dose, 4-way crossover of LEV IR oral tablet 250 mg; LEV 250 (drug substance) delivered to proximal small bowel via [redacted] capsule; LEV 250 mg (drug substance) delivered to distal small bowel via [redacted] capsule; LEV 250 mg (drug substance) delivered to ascending colon via [redacted] capsule in healthy male volunteers (18 to 65 years, inclusive). b(4) |
| N01140 | 12 (12) | 16-Mar-2005 – 25-May-2005 / France | Single dose, open-label pilot study to compare the pharmacokinetics of LEV 500 mg from 3 XR test formulations with the IR reference formulation in healthy volunteers and to assess the influence of food on one of the test formulations (pilot bioequivalence study). |
| N01160 | 24 (24) | 04-Jul-2006 – 02-Sep-2006 / France | Randomized, open-label, three-way crossover study of LEV XR (1000 mg, once daily) and LEV IR (500 mg B.I.D.). Single and multiple dose bioequivalence and assessment of food effect on LEV XR in healthy volunteers. |
| N01260 | 24 (24) | 05-Jan-2007 – 26-Feb-2007 / France | Randomized, open-label, single dose, three-way crossover dose proportionality study of LEV XR 1000 mg, 2000 mg, and 3000 mg, in healthy volunteers. |

### 2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

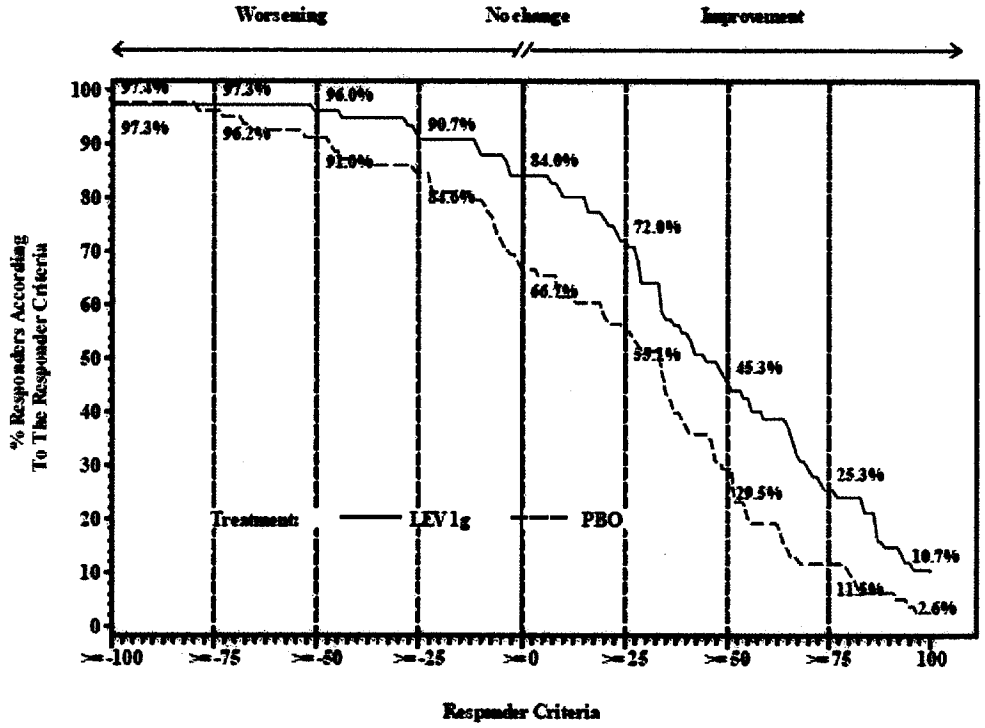
The primary endpoint in the double-blind, placebo controlled, randomized safety and efficacy trial was the median percent reduction in partial onset seizure (Type I) frequency per week over the Treatment Period from Baseline. Active treatment and placebo were used as add-on therapy to the existing regimen. While reduction in seizure frequency is a reasonable endpoint for an anti-seizure agent, a significant increase in the number of responders (≥50% reduction in seizure frequency) would be a desirable outcome for any drug with this indication.

Median percent reduction in seizures were 46.1% in LEV XR *vs.* 33.4% in PBO. The estimated percent reductions over PBO in partial onset seizure (Type I) frequency per week over the Treatment Period was 14.4% in the ITT population; this reduction over PBO was statistically significant at the 2-sided 5% significance level (p = 0.038). This percent reduction increased to 18.6% (p = 0.003) after excluding the subjects with major protocol deviations [10 subjects (12.7%) in the PBO group; 11 (13.9%) in the LEV XR group]. Since there were few Type II and Type III seizures, the results on total seizures (Type I + II + III) were very similar to those on partial seizure (Type I).

The absolute and percent reduction from baseline in either partial onset (Type I) or total (Type I + II + III) seizure frequency per week over the Treatment Period yielded similar results in favor of LEV XR over PBO, all significant at the 2-sided 5% significance level. The median difference between LEV XR and PBO for the percent reduction from baseline in partial seizure frequency was 21.9% (95% 2-sided CI [7.3% - 36.7%]; p=0.002).

The proportion of responders (patients having $\geq$50% reduction in seizure frequency) in partial onset seizure (Type I) frequency per week over the Treatment Period was higher after LEV XR (43.0%) than after PBO (29.1%); this difference in favor of LEV XR was not statistically significant (p = 0.070) at the 5% significance level. The odds ratio (OR) with a 95% 2-sided CI was 1.84 [0.95 - 3.55].

Figure 2:2 N01235: Plot Of The Percentage Of Responders As A Function Of An Increasing Responder Criteria




## 2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes; see Section 2.6

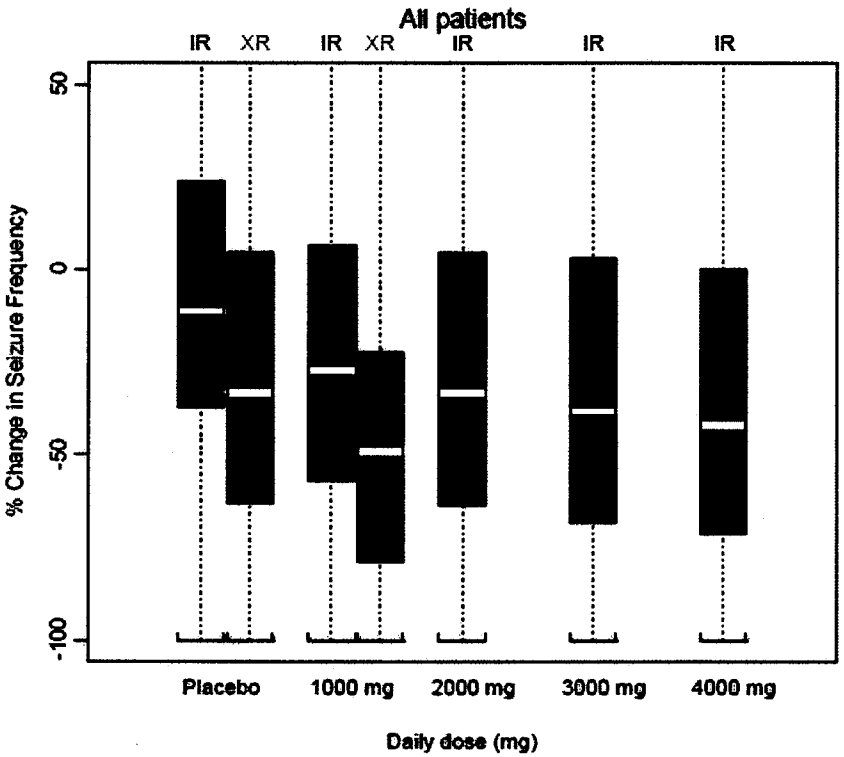
## 2.2.4 Exposure-response

Since this is a Type 3 new formulation study, the primary response criteria in the randomized double-blind placebo-controlled study was efficacy (reduction in seizure frequency) and safety. Single plasma concentrations were collected on visits 5, 6 and 7 in the clinical study.

Dosing-response relationships have been evaluated. The % change in seizure frequency versus dose is shown below for the placebo and 1000 mg dosage for both the IR and the Keppra XR products (below). An additional analysis separated improving and deteriorating patients

for both the IR and XR products, and suggested that the Keppra XR product had more improving patients than the Keppra IR product.

**Figure 10:11** **Predicted dose-response relationship after IR (dark red) and XR (orange) administration with box-plots for the percentage change in seizure frequency from baseline as a function of daily dose.**




**2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy*? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.**

Exposure response was not measured for this product in the clinical study N01235. Previous studies in patients have not identified a clear therapeutic range for levetiracetam, possibly because of the frequent use of this drug with other anti-epileptic drugs. Therefore the effect of any one agent in a complex regimen is difficult to discern.

Trough concentrations were measured on up to three different occasions during N01235, and this was the basis for comparisons that are made in the analysis between (a) adolescents and adults, and between (b) different ethnic groups.

### 2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety*? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

No clinical relationships between plasma concentrations and drug safety have been established.

### 2.2.4.3 Does this drug prolong the QT or QTc interval?

The original NDA did not find any QTc interval abnormalities with LEV. There have also been no postmarketing concerns related to EKG abnormalities. The following table is the ECG evaluation from the original NDA:

**Table 73: ECG Interval Evaluation in Controlled Studies of Epilepsy (N051, N132, and N138)**

| Interval (units) | Levetiracetam n = 596 | Placebo n = 301 |
|---|---|---|
| PR Interval (msec) | | |
| Mean change from baseline | 1.0 | 0.2 |
| Shift analysis (WNL – WNL) | 97.3% | 96.3% |
| Percent change from baseline[a] | 0.7% | 1.7% |
| QRS Interval (msec) | | |
| Mean change from baseline | 0.5 | 0.7 |
| Shift analysis (WNL – WNL) | 92.4% | 89.7% |
| Percent change from baseline | 0 | 1.3% |
| QTc Interval (msec) | | |
| Mean change from baseline | -1.5 | -2.7 |
| Shift analysis (WNL – WNL) | 96.8% | 97.3% |
| Percent change from baseline | 0.5% | 0.3% |
| Rate (bpm) | | |
| Mean change from baseline | -1.1 | -0.8 |
| Shift analysis (WNL – WNL) | 65.8% | 73.8% |
| Percent change from baseline | 16.8% | 19.3% |

[a]Percent of patients with a possibly clinically significant change from baseline

### 2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes, the dosing is following the regimen previously approved for the immediate release product. [redacted] In fact, the limited information indicates that exposure is 77% higher in adolescents compared to adults. Therefore, b(4)

a properly designed pharmacokinetic study in this age group is necessary [redacted] b(4)

### 2.2.5 What are the PK characteristics of the drug and its major metabolite?

LEV is rapidly and almost completely (>95%) absorbed following oral ingestion with Tmax occurring at **1.3–5.2 hours. LEV pharmacokinetics is linear in the range of 500–5000 mg** with steady state serum levels **occurring within 24–48 h after initiation** of therapy. The mean half-life (t1/2) **of LEV in serum is 6–13.3 h.** LEV enters the cerebrospinal fluid **(CSF) with a Tmax of 3–7.3 hr. Efflux of LEV from the CSF takes twice** as long as that from the blood (t1/2 of 24 hours), which may explain prolonged anticonvulsant activity even when LEV serum concentrations are low.

Metabolism of LEV is minimal, and excretion occurs almost completely through urine. Approximately 34% of the administered dose of LEV is **metabolized and 66% is recovered unchanged in urine. LEV's** clearance is in relation to creatinine clearance, with >90% of the drug being excreted within 48 h. LEV is filtered by the glomeruli and undergoes partial tubular reabsorption. An amidase in blood hydrolyzes LEV to a pharmacologically inactive metabolite.

### 2.2.5.1 What are the single dose and multiple dose PK parameters and how do these compare to the IR product?

Study NO1160 includes both an initial 24 hr PK study and followup at 9 days of therapy in 24 healthy subjects. Below are shown the plots for first day (upper plot) and days 6-9 (lower plot). Trough concentrations on days 6, 7, and 8 are consistent with steady state, and the concentration-time profile is similar on days 1 and 9. Table 11:4 below shows the comparison of Keppra XR and IR.

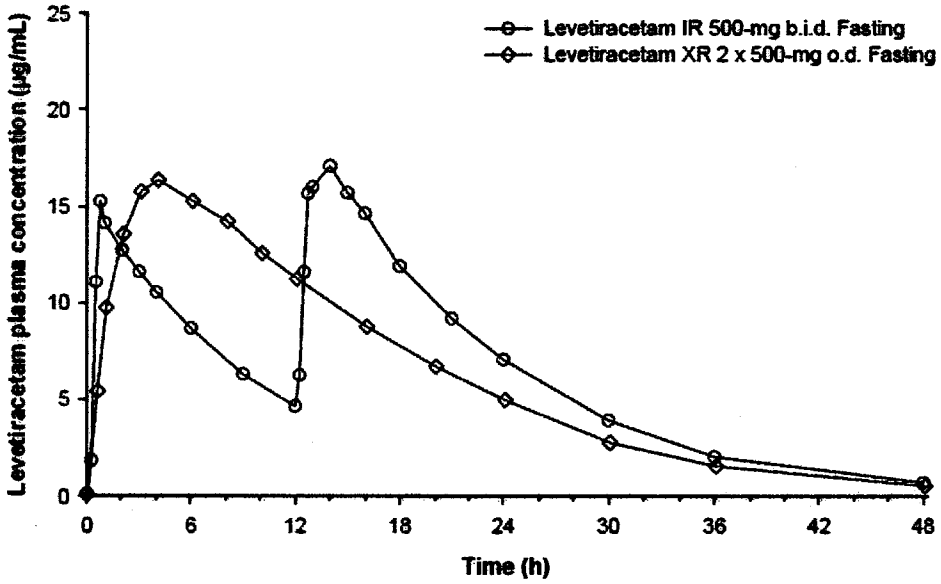
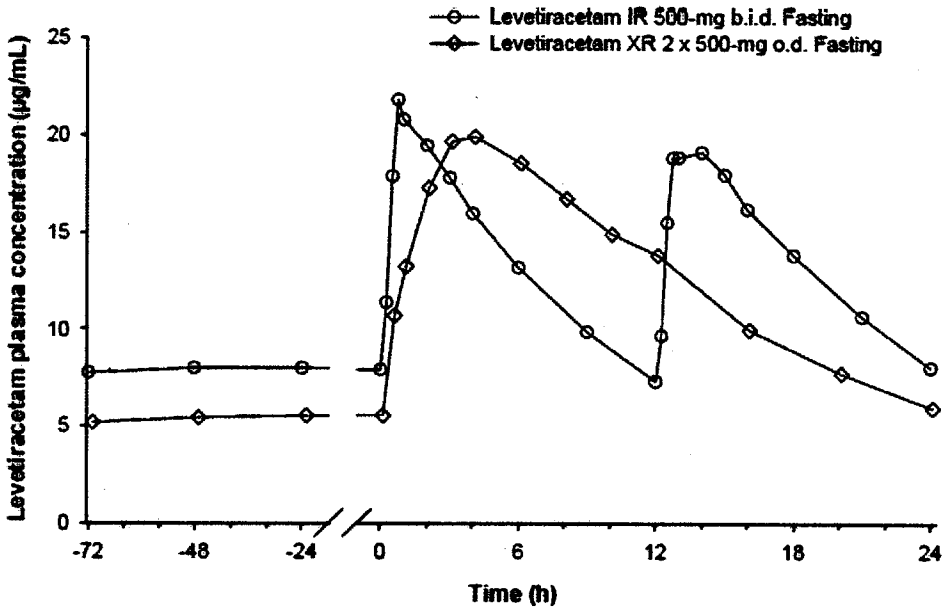



Table 11:4 Summary of Main PK Parameters of IR and XR Formulations under Fasting Conditions on Day 9 after Repeated Administration, Overall and by Gender – PP Population

| Parameter | Both Sexes (N=24) | | Males (N=12) | | Females (N=12) | |
|---|---|---|---|---|---|---|
| | IR tablet[a] | XR tablet[a] | IR tablet[a] | XR tablet[a] | IR tablet[a] | XR tablet[a] |
| $C_{max}$ (µg/mL) | 25.6 (18.6) | 21.3 (14.2) | 23.2 (14.6) | 19.8 (11.3) | 28.2 (17.1) | 22.9 (13.3) |
| $t_{max}$ (h)[b] | 0.75 (0.25-2.00) | 4.00 (2.00-6.00) | 0.75 (0.25-2.00) | 4.00 (2.00-6.00) | 0.75 (0.25-2.00) | 3.50 (3.00-6.00) |
| AUC(0-24) (µg.h/mL) | 327 (15.9)[c] | 309 (13.3) | 301 (13.1) | 286 (9.13) | 358 (13.8)[d] | 334 (12.3) |
| $C_{av}$ (µg/mL) | 13.6 (15.8)[c] | 12.9 (13.3) | 12.5 (13.1) | 11.9 (9.13) | 14.9 (13.6)[d] | 13.9 (12.3) |
| PTF (-) | 1.27 (21.5)[c] | 1.19 (11.7) | 1.24 (23.6) | 1.17 (10.5) | 1.30 (19.7)[d] | 1.21 (13.0) |
| $MRT_{eml}$ (h) | 10.6 (25.2)[c] | 10.1 (23.1) | 10.9 (31.9) | 9.71 (25.8) | 10.4 (16.6)[d] | 10.5 (20.4) |
| $C_{min}$ (µg/mL) | 8.02 (21.9)[c] | 5.93 (17.2) | 7.39 (20.5) | 5.88 (14.6) | 8.76 (20.6)[d] | 5.99 (20.1) |
| $T_{50\%Cmax}$ (h) | 12.4 (26.3) | 14.8 (14.0) | 13.0 (27.1) | 14.9 (12.0) | 11.8 (25.4) | 14.8 (16.3) |
| $T_{75\%Cmax}$ (h) | 3.41 (67.1) | 7.79 (27.1) | 3.44 (75.0) | 7.41 (26.7) | 3.39 (61.3) | 8.18 (27.6) |

[a] Geometric means (CV%), median (range) for $t_{max}$ and arithmetic means (CV%) for $T_{50\%Cmax}$ and $T_{75\%Cmax}$
[b] $t_{max}$ is the time from the latest administration before $C_{max}$
[c] N=23 and [d] N=11: Subject 0022 had 2 missing samples at the end of the profile
Source: Table 14.2.1:9 and Table 14.2.1:10




### 2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The present study had no direct comparisons of patient and healthy subject profiles. However, trough concentrations were obtained from patients receiving Keppra XR, and this can be descriptively compared with trough concentrations in healthy subjects given the same dosage of Keppra XR over 9 days. Trough levels in adult patients, who were receiving multiple drugs, averaged 10 mcg/ml while the trough concentrations in healthy subjects averaged about 5 mcg/ml. The reason for this difference is presently unknown, but this concentration in patients falls into the range of trough concentrations observed after the LEV IR formulation (see below).

Additional comparisons can be made both by comparing the previous experience with trough blood levels of levetiracetam in patients given the IR form of the drug, and with patients on Keppra XR in the N0-1235 study. The IR form of the drug would be expected to produce higher trough levels, since the product is given twice daily.

In a clinical study in 2007 of therapeutic drug monitoring with Keppra IR tablets, responders had 12-hour **trough concentrations of 4.6 – 21** mcg/ml. The definition of response was the same as in the clinical study N0-1235. Other investigators have stated that the therapeutic range of trough concentrations is **5 – 30 mcg/ml. The most frequent** adverse effects of Keppra (asthenia, headache, somnolence, insomnia, dizziness, and memory impairment) are not related to plasma concentrations of the drug.

Given that information, it would appear that the trough concentrations of levetiracetam after Keppra XR observed in study NO-1235 are within the range of trough concentrations previously established for Keppra IR product (see Table below).

**Table 2:12 Study Drug Plasma Concentration at Visits 5, 6, and 7 – N01235 Safety Population**

| Visit | Statistics | LEV XR N=77 | |
|---|---|---|---|
| | | [Plasma] mcg/mL | Sampling time (hour)[a] |
| Visit 5 | n | 68 | 71 |
| | Mean (SD) | 10.96 (4.61) | 24.74 (79.74) |
| | Median | 11.00 | 14.00 |
| | Min - Max | 1.0 - 26.0 | 10.5 - 686.0 |
| Visit 6 | n | 70 | 71 |
| | Mean (SD) | 11.20 (3.81) | 14.74 (2.72) |
| | Median | 11.0 | 14.00 |
| | Min - Max | 3.0 - 24.0 | 11.0 - 25.4 |
| Visit 7 | n | 66 | 71 |
| | Mean (SD) | 11.70 (5.97) | 16.28 (8.37) |
| | Median | 11.00 | 14.67 |
| | Min - Max | 2.0 - 33.0 | 10.3 - 73.3 |

[a] Time in hours from last dose intake time to plasma sampling time.
Source: N01235 CSR Table 14.1.6.2

### 2.2.5.3 What are the characteristics of drug absorption?

Previous literature studies show that LEV is rapidly and almost completely absorbed (>95%) following oral ingestion with a Tmax of **1.3–5.2 hours.**

The mean $t_{max}$ for the Keppra XR and the Keppra IR tablets are 4.0 and 0.88 hours respectively. As shown in the table below, the $t_{max}$ for Keppra XR can be as early as 2.0 hours and as late as 10.0 hours.

**Table 11:2 Summary of Main PK Parameters of IR and XR Formulations under Fasting Conditions after a Single Daily Dose, Overall and by Gender – PP Population**

| Parameter | Both Sexes (N=24) | | Males (N=12) | | Females (N=12) | |
|---|---|---|---|---|---|---|
| | IR tablet[a] | XR tablet[a] | IR tablet[a] | XR tablet[a] | IR tablet[a] | XR tablet[a] |
| $C_{max}$ (µg/mL) | 19.7 (17.1) | 17.4 (17.9) | 18.7 (20.3) | 15.1 (12.6) | 20.7 (11.7) | 20.2 (6.21) |
| $t_{max}$ (h)[b] | 0.88 (0.50-3.03) | 4.00 (2.00-10.00) | 0.88 (0.50-2.00) | 4.00 (2.00-6.00) | 0.88 (0.50-3.03) | 4.00 (3.00-10.00) |
| AUC(0-t) (µg h/mL) | 317 (13.9) | 307 (15.1) | 292 (11.4) | 279 (12.5) | 345 (10.8) | 338 (10.5) |
| AUC (µg h/mL) | 325 (13.8) | 313 (15.1) | 300 (11.5) | 285 (12.7) | 353 (11.0) | 344 (10.7) |
| $t_{\frac{1}{2}}$ (h) | 7.28 (12.1) | 7.60 (10.0) | 7.60 (11.4) | 7.82 (7.35) | 6.97 (11.6) | 7.39 (11.8) |

[a] Geometric means (CV%) and median (range) for $t_{max}$
[b] $t_{max}$ is the time from the latest administration before $C_{max}$
Source: Table 14.2.1:6 and Table 14.2.1:7

### 2.2.5.4 What are the characteristics of drug distribution?

LEV and its major metabolite (inactive) are less than 10% bound to plasma proteins. LEV enters the cerebrospinal fluid (CSF) with a **Tmax of 3–7.3 hours. The mean t1/2** of LEV in CSF is 24 hours which is approximately double that of the plasma t1/2.

### 2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

These studies were not part of this submission, but have been established through previous studies of the parent drug.

### 2.2.5.6 What are the characteristics of drug metabolism?

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24% of dose) and is not dependent on any liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

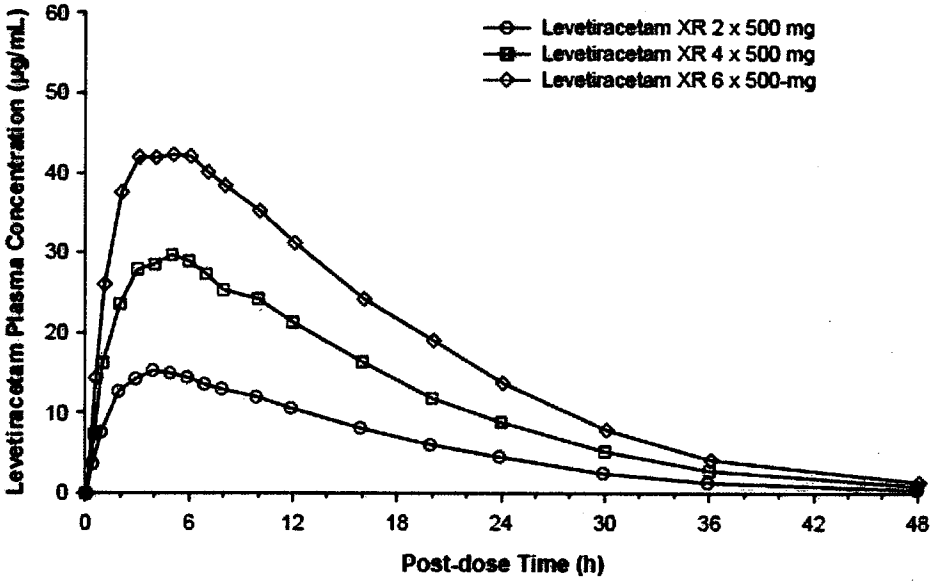
### 2.2.5.7 What are the characteristics of drug excretion?

Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active secretion in the kidney.

### 2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

From the published literature, LEV displays linearity in the range of **500–5000 mg and dose-proportional pharmacokinetics.**

From the dose proportionality study in this submission, study NO-1260 demonstrated that Keppra XR 1000 mg, 2000 mg, and 3000 mg were dose proportional in healthy subjects. The following Figure and Table present the findings of NO-1260.




PK parameters derived from the individual concentration profiles are summarized below:

| Parameter (N=24) | Levetiracetam XR dose | | | Slope of the regression[b] | |
|---|---|---|---|---|---|
| | 2 x 500 mg[a] | 4 x 500 mg[a] | 6 x 500 mg[a] | Point Estimate | 90% CI |
| $C_{max}$ (µg/mL) | 16.2 (20.7) | 31.5 (18.8) | 46.2 (20.6) | 0.953 | (0.907 ; 0.999) |
| $t_{max}$ (h) | 4.50 (2.00-8.00) | 5.00 (2.00-10.00) | 4.50 (2.00-10.00) | NC | NC |
| AUC(0-t) (µg.h/mL) | 280 (17.6) | 559 (17.0) | 839 (15.9) | 0.998 | (0.973 ; 1.02) |
| AUC (µg.h/mL) | 285 (17.6) | 570 (17.1) | 855 (16.1) | 0.998 | (0.973 ; 1.02) |
| $t_{½}$ (h) | 7.26 (12.1) | 7.33 (14.1) | 7.15 (13.1) | -0.0120 | (-0.0443 ; 0.0202) |
| CL/F (mL/min) | 58.4 (17.6) | 58.5 (17.1) | 58.5 (16.1) | 0.00174 | (-0.0234 ; 0.0268) |
| $V_z$/F (L) | 36.7 (22.0) | 37.1 (21.3) | 36.2 (18.0) | -0.0103 | (-0.0504 ; 0.0298) |

[a] Geometric means (geometric CV%) and median (range) for $t_{max}$
[b] Linear regression between log-transformed parameter and log-transformed dose
NC: not calculated

## 2.2.5.9 How do the PK parameters change with time following chronic dosing?

As can be seen from the Tables below, the tmax and AUC after Keppre XR are similar between the single dose study (Table 11.2) and after multiple doses on day 9 (Table 11.4). The Cmax increased somewhat, as would be expected at steady state. The Cmin for Keppra XR was lower than the Cmin for IR Keppra on chronic dosing.

Table 11:2 **Summary of Main PK Parameters of IR and XR Formulations under Fasting Conditions after a Single Daily Dose, Overall and by Gender – PP Population**

| Parameter | Both Sexes (N=24) | | Males (N=12) | | Females (N=12) | |
|---|---|---|---|---|---|---|
| | IR tablet[a] | XR tablet[a] | IR tablet[a] | XR tablet[a] | IR tablet[a] | XR tablet[a] |
| $C_{max}$ (µg/mL) | 19.7 (17.1) | 17.4 (17.9) | 18.7 (20.3) | 15.1 (12.6) | 20.7 (11.7) | 20.2 (6.21) |
| $t_{max}$ (h)[b] | 0.88 (0.50-3.03) | 4.00 (2.00-10.00) | 0.88 (0.50-2.00) | 4.00 (2.00-6.00) | 0.88 (0.50-3.03) | 4.00 (3.00-10.00) |
| AUC(0-t) (µg.h/mL) | 317 (13.9) | 307 (15.1) | 292 (11.4) | 279 (12.5) | 345 (10.8) | 338 (10.5) |
| AUC (µg.h/mL) | 325 (13.8) | 313 (15.1) | 300 (11.5) | 285 (12.7) | 353 (11.0) | 344 (10.7) |
| $t_{½}$ (h) | 7.28 (12.1) | 7.60 (10.0) | 7.60 (11.4) | 7.82 (7.35) | 6.97 (11.6) | 7.39 (11.8) |

[a] Geometric means (CV%) and median (range) for $t_{max}$
[b] $t_{max}$ is the time from the latest administration before $C_{max}$
Source: Table 14.2.1:6 and Table 14.2.1:7

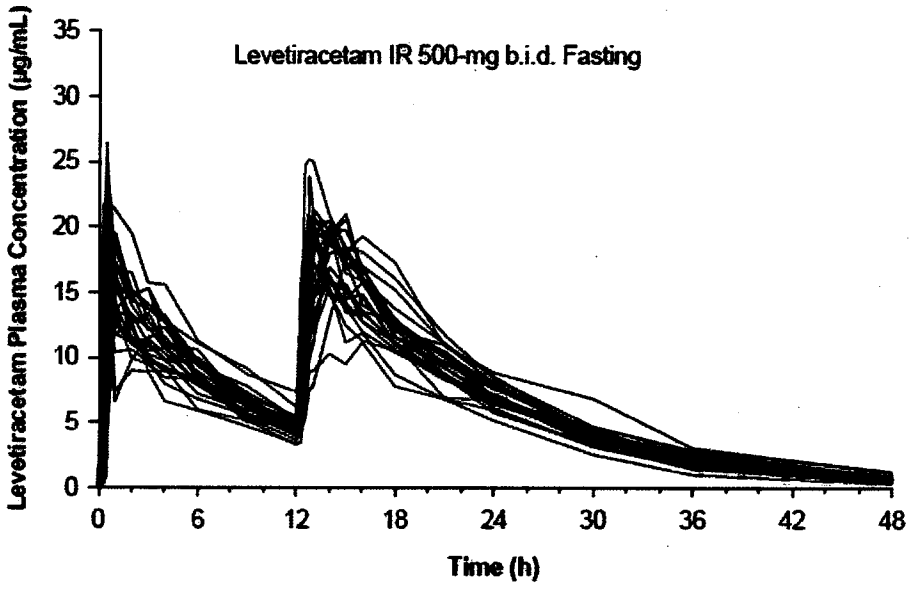
Table 11:4 **Summary of Main PK Parameters of IR and XR Formulations under Fasting Conditions on Day 9 after Repeated Administration, Overall and by Gender – PP Population**

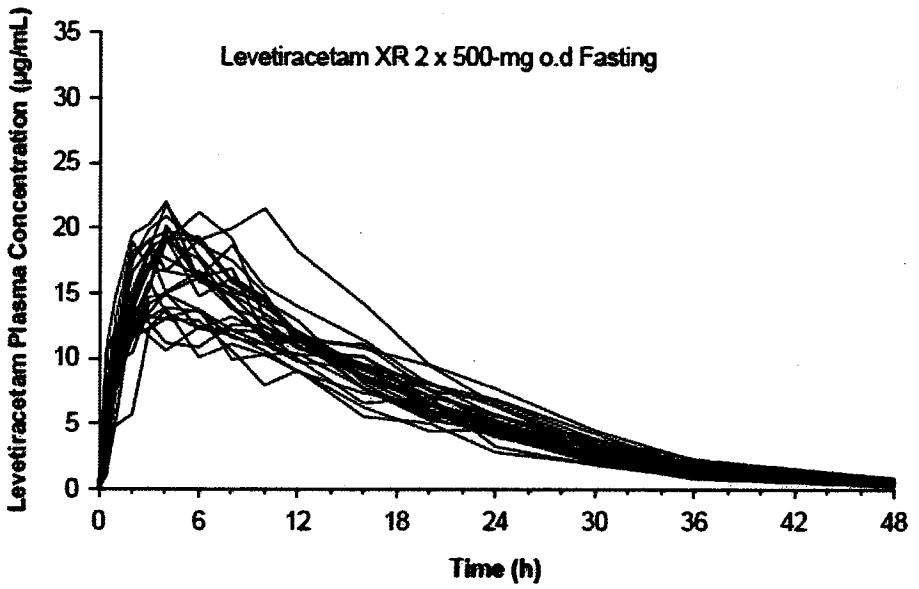
| Parameter | Both Sexes (N=24) | | Males (N=12) | | Females (N=12) | |
|---|---|---|---|---|---|---|
| | IR tablet[a] | XR tablet[a] | IR tablet[a] | XR tablet[a] | IR tablet[a] | XR tablet[a] |
| $C_{max}$ (µg/mL) | 25.6 (18.6) | 21.3 (14.2) | 23.2 (14.6) | 19.8 (11.3) | 28.2 (17.1) | 22.9 (13.3) |
| $t_{max}$ (h)[b] | 0.75 (0.25-2.00) | 4.00 (2.00-6.00) | 0.75 (0.25-2.00) | 4.00 (2.00-6.00) | 0.75 (0.25-2.00) | 3.50 (3.00-6.00) |
| AUC(0-24) (µg.h/mL) | 327 (15.9)[c] | 309 (13.3) | 301 (13.1) | 286 (9.13) | 358 (13.8)[d] | 334 (12.3) |
| $C_{trr}$ (µg/mL) | 13.6 (15.8)[c] | 12.9 (13.3) | 12.5 (13.1) | 11.9 (9.13) | 14.9 (13.6)[d] | 13.9 (12.3) |
| PTF (-) | 1.27 (21.5)[c] | 1.19 (11.7) | 1.24 (23.6) | 1.17 (10.5) | 1.30 (19.7)[d] | 1.21 (13.0) |
| $MRT_{eml}$ (h) | 10.6 (25.2)[c] | 10.1 (23.1) | 10.9 (31.9) | 9.71 (25.8) | 10.4 (16.6)[d] | 10.5 (20.4) |
| $C_{min}$ (µg/mL) | 8.02 (21.9)[c] | 5.93 (17.2) | 7.39 (20.5) | 5.88 (14.6) | 8.76 (20.6)[d] | 5.99 (20.1) |
| $T_{50\%Cmax}$ (h) | 12.4 (26.3) | 14.8 (14.0) | 13.0 (27.1) | 14.9 (12.0) | 11.8 (25.4) | 14.8 (16.3) |
| $T_{75\%Cmax}$ (h) | 3.41 (67.1) | 7.79 (27.1) | 3.44 (75.0) | 7.41 (26.7) | 3.39 (61.3) | 8.18 (27.6) |

[a] Geometric means (CV%), median (range) for $t_{max}$, and arithmetic means (CV%) for $T_{50\%Cmax}$ and $T_{75\%Cmax}$
[b] $t_{max}$ is the time from the latest administration before $C_{max}$
[c] N=23 and [d] N=11: Subject 0022 had 2 missing samples at the end of the profile
Source: Table 14.2.1:9 and Table 14.2.1:10

## 2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

A certain amount of variability is due to the dosage form, as is evidenced by a comparison between the 500 mg IR formulation every 12 hours in healthy subjects (upper figure below) and the 500 mg XR formulation X 2 tablets (lower figure below). The CV% for Cmax for the XR formulation is 17.9, and for the IR dosage form is 17.1. The CV% for AUC is 15.1 for Keppra XR, and 13.8 for Keppra IR. The cause of this variability is unknown. The amount of variation in plasma concentrations between healthy subjects is shown by the following spaghetti plots:




### 2.2.6 Is the proposed dose conversion from the Keppra IR to Keppra XR acceptable?

No explanation about the conversion from the IR to the XR product is suggested in the labeling. Seizure patients in N01235 were switched back and forth from the IR to the XR product so it appears that this would not present a significant risk to patients.

## *2.3. Intrinsic Factors*

**2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?**

Multiple factors influence LEV pharmacokinetics, including body weight and renal function. Other differences in PK, based upon body weight and renal function, can be seen in women (20% higher AUC than men), pediatric patients (40% higher body-weight adjusted clearance), and severe hepatic impairment (clearance 50% of normal, mostly secondary to decreased renal function). See current Keppra label for this information.

**2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

See current Keppra label.

### 2.3.2.1 Elderly

As per the previous Keppra label, pharmacokinetics of levetiracetam were evaluated in 16 subjects (age 61-88 years) with creatinine clearance ranging from 30 to 74 mL/min. Following oral administration of twice-daily dosing for 10 days, total body clearance decreased by 38% and the half-life was 2.5 hours longer in the elderly compared to healthy adults. This is most likely due to the decrease in renal function in these subjects.

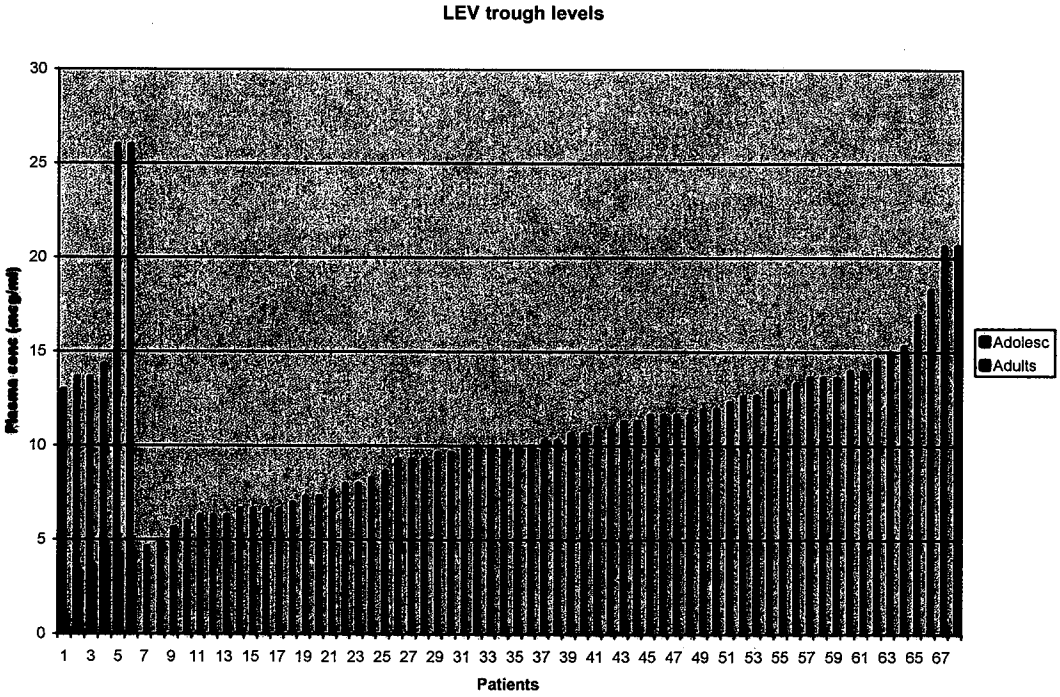
The age range [redacted] is from 12 to 70 years of age, and elderly is defined as over the age of 65 years old. This drug is likely to be used in patients over 65 years of age, where renal function will affect LEV elimination and dosing. Publications in the literature attest to the fact that LEV is used in this patient population. Therefore a postmarketing pharmacokinetic study of Keppra XR in the elderly is needed so that a definite initial dosing recommendation can be made for the elderly.

b(4)

**2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?**

[redacted] b(4)

. In clinical study N0-1235, 16 patients under the age of 18 years old were recruited, including 12 patients under the age of 16 years old. Of the 16 patients under the age of 18 years old, 7 received Keppra XR and 9 received placebo. Trough concentrations on at least 2 occasions were provided for 6 adolescents (12-16 years of age) and 68 adults. As can be demonstrated by the Figure and Table below, the trough LEV concentrations were 77% higher in the adolescent patients.




t-Test: Two-Sample Assuming Equal Variances

LEV trough conc in patients treated with Keppra XR 500 mg X 2 once daily

| | *Adolescents* | *Adults* |
|---|---|---|
| Mean (mcg/ml) | 17.77777778 | 10.04166667 |
| Variance | 40.74074074 | 15.57908379 |
| Observations | 6 | 68 |
| Pooled Variance | 17.32642108 | |
| Hypothesized Mean Difference | 0 | |
| Df | 72 | |
| t Stat | 4.363977352 | |
| P(T<=t) one-tail | 2.0961E-05 | |
| t Critical one-tail | 1.666293697 | |
| P(T<=t) two-tail | 4.19219E-05 | |

| t Critical two-tail | 1.993463539 |
|---|---|

**The Keppra IR product is labeled for children 6 – 16 years old to receive** 20 mg/kg/day as the initial dose. The adolescents in the N0-1235 study **did in fact receive 12.5 – 20 mg/kg/day**, so weight alone does not explain why trough concentrations were higher in the adolescents. Pharmacokinetic studies in children **in the age range of 6 – 12 years old** found them to have a 40% higher clearance per body weight than adults. This finding would suggest that the LEV trough concentrations should be lower in pediatric patients than that of the adults. Therefore the present finding of higher LEV troughs in the adolescent patients cannot be explained by current published literature with the IR formulation.

A pharmacokinetics study would have to be performed in the adolescent age group before an appropriate dose of Keppra XR can be determined for future drug labeling.

### 2.3.2.3 Gender

Since apparent clearance of LEV is weight related, women have a lower clearance rate (higher Cmax and AUC) than men. Clearances adjusted for body weight were comparable.

### 2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians; and Collection of Race and Ethnicity Data in Clinical Trials, is an important co-variate and should be discussed.

LEV trough concentrations after Keppra XR in the Hispanic patients (n=13) in N0-1235 were 40% higher ($p<0.011$, T test, see Table below) than trough concentrations in Caucasian patients (n=37). The Indian/Pakistani patients had intermediate trough concentrations, so were not significantly different from either of the other two ethnic groups.

t-Test: Two-Sample Assuming Equal Variances
LEV trough plasma levels

| | *Caucasian* | *Hispanic* |
|---|---|---|
| Mean | 9.837837838 | 13.76923077 |
| Variance | 14.04704705 | 44.84045584 |
| Observations | 37 | 13 |
| Pooled Variance | 21.74539925 | |
| Hypothesized Mean Difference | 0 | |
| Df | 48 | |
| t Stat | -2.614871163 | |
| P(T<=t) one-tail | 0.005946124 | |
| t Critical one-tail | 1.677224197 | |

| | |
|---|---|
| P(T<=t) two-tail | 0.011892249 |
| t Critical two-tail | 2.010634722 |

The sponsor has not previously pursued differences in ethnicity with LEV, and only lists a small trial of 12 Caucasians and 12 Asians previously in Keppra labeling. There were no Hispanic normal subjects included in the pivotal trial (N0-1160) in this submission. In consideration of the present finding, we recommend that the sponsor review the information available on the pharmacokinetics and safety of LEV in the Hispanic population compared to the Caucasian population.

### 2.3.2.5 Renal impairment

Dosing in renal impairment for Keppra is based upon creatinine clearance calculated by the Cockroft-Gault formula from serum creatinine. The following table is taken from the present Keppra IR label:

**Table 15: Dosing Adjustment Regimen For Adult Patients With Impaired Renal Function**

| Group | Creatinine Clearance (mL/min) | Dosage (mg) | Frequency |
|---|---|---|---|
| Normal | > 80 | 500 to 1,500 | Every 12 h |
| Mild | 50 – 80 | 500 to 1,000 | Every 12 h |
| Moderate | 30 – 50 | 250 to 750 | Every 12 h |
| Severe | < 30 | 250 to 500 | Every 12 h |
| ESRD patients using dialysis ---- | | 500 to 1,000 | [1]Every 24 h |

[1] Following dialysis, a 250 to 500 mg supplemental dose is recommended.

No studies or simulations with Keppra XR have been performed in renally impaired patients [redacted] Since the IR dosage form already carries a dosage interval of every 24 hours for end stage renal disease (ESRD) patients on dialysis, Keppra XR should not be labeled for use in renal dialysis patients.

b(4)

### 2.3.2.6 Hepatic impairment

Previous Keppra labeling states that severe hepatic impairment may decrease total body clearance by 50%, and that most of that change is based upon decreased renal clearance.

**2.3.2.7 What pregnancy and lactation use information is there in the application? Other human factors that are important to understanding the drug's efficacy and safety?**

Current labeling states: **"Pregnancy Category C**
In animal studies, levetiracetam produced evidence of developmental toxicity at doses similar to or greater than human therapeutic doses. Administration to female rats throughout pregnancy and lactation was associated with increased incidences of minor fetal skeletal abnormalities and retarded offspring growth pre- and/or postnatally at doses ≥350 mg/kg/day (approximately equivalent to the maximum recommended human dose of 3000 mg [MRHD] on a mg/m2 basis) and with increased pup mortality and offspring behavioral alterations at a dose of 1800 mg/kg/day (6 times the MRHD on a mg/m2 basis). The developmental no effect dose was 70 mg/kg/day (0.2 times the MRHD on a mg/m2 basis). There was no overt maternal toxicity at the doses used in this study. Treatment of pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and increased incidences of minor fetal skeletal abnormalities at doses ≥600 mg/kg/day (approximately 4 times MRHD on a mg/m2 basis) and in decreased fetal weights and increased incidences of fetal malformations at a dose of 1800 mg/kg/day (12 times the MRHD on a mg/m2 basis). The developmental no effect dose was 200 mg/kg/day (1.3 times the MRHD on a mg/m2 basis). Maternal toxicity was also observed at 1800 mg/kg/day. When pregnant rats were treated during the period of organogenesis, fetal weights were decreased and the incidence of fetal skeletal variations was increased at a dose of 3600 mg/kg/day (12 times the MRHD). 1200 mg/kg/day (4 times the MRHD) was a developmental no effect dose. There was no evidence of maternal toxicity in this study.

Treatment of rats during the last third of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m2 basis). There are no adequate and well-controlled studies in pregnant women. KEPPRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

KEPPRA Pregnancy Registry
UCB, Inc. has established the KEPPRA Pregnancy Registry to advance scientific knowledge about safety and outcomes associated with pregnant women being treated with KEPPRA. To ensure broad program access and reach, either a healthcare provider or the patient can initiate enrollment in the KEPPRA Pregnancy Registry by calling (888) 537-7734 (toll free). Patients may also enroll in the North American Antiepileptic Drug Pregnancy Registry by calling **(888) 233-2334 (toll free)."**

This wording should be included in the labeling for the new formulation Keppra XR.

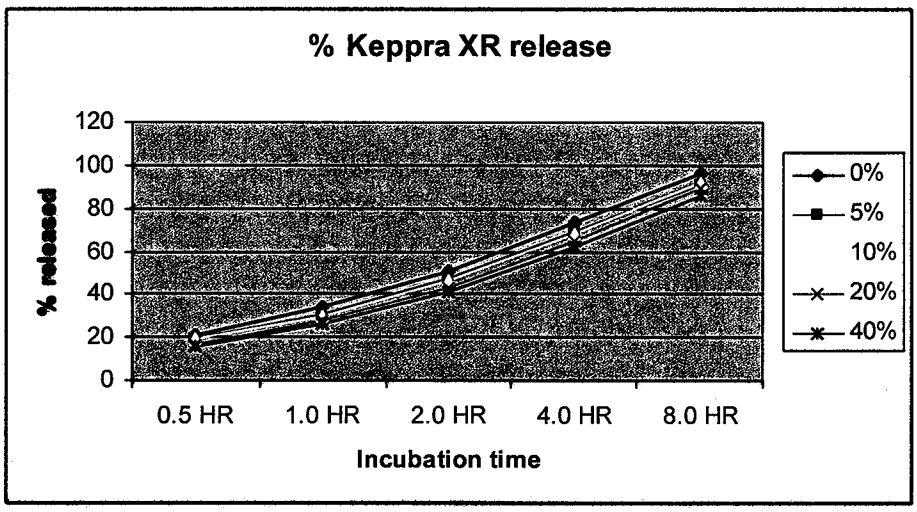
## *2.4. Extrinsic Factors*

### 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Dose dumping with alcohol was examined in vitro with concentrations from **0 – 40% alcohol. The method used a 0.05M phosphate buffer pH=6.0 as** the release medium, which is the selected dissolution medium for this product. The similarity (f2) of each alcohol concentration was as follows:

Control vs. 5% ethanol - f2 = 69.4
Control vs. 10% ethanol - f2 = 67.3
Control vs. 20% ethanol - f2 = 57.5
Control vs. 40% ethanol - f2 = 51.4

Where an f2 > 50 is acceptable. The figure for control versus percent ethanol is as follows with the Keppra XR tablet:




In vitro data indicate that there is no significant dose dumping potential with alcohol.

### 2.4.2 Drug-drug interactions

Keppra has an extensive drug-drug interaction section in the present label, and that information should be presented in the Keppra XR label.

**2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?**

None.

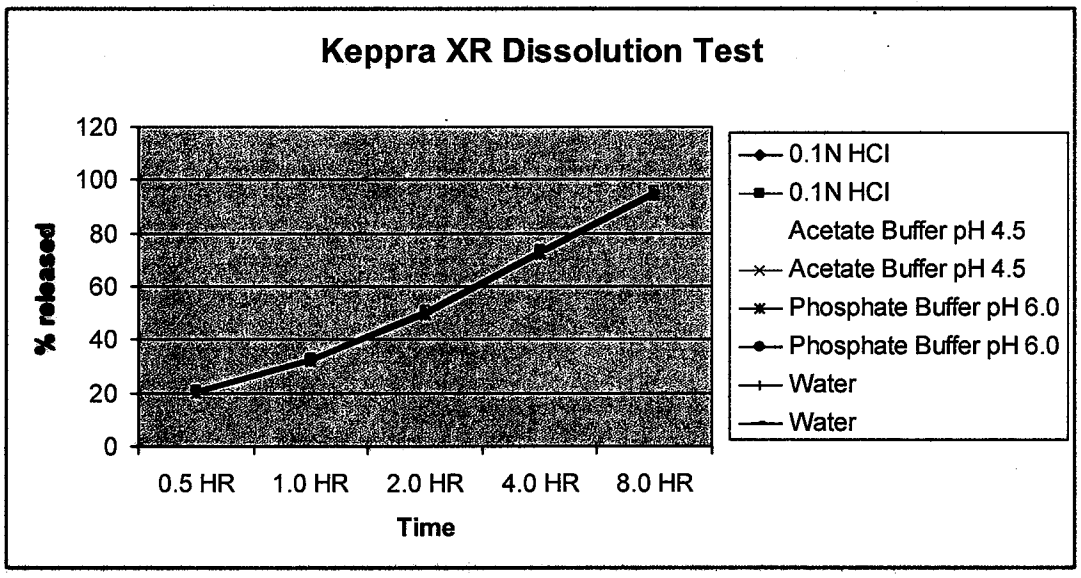
**2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?**

The unresolved issues have been identified as (a) adolescent dosing, (b) dosing in the elderly, and (c) altered PK in the Hispanic patient population.

***2.5. General Biopharmaceutics*** This section should summarize the salient points about the attributes of the drug product.

**2.5.1 Dissolution profiles**

An average of 95% of LEV was released from the Keppra XR tablets in 8 hours under the conditions of the dissolution test. The experiment was repeated under 4 conditions with 12 observations per experiment. The dissolution conditions and profile are as follows:




**2.5.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**

The relative bioavailability comparison table for the Keppra XR and Keppra IR products under fasting conditions after repeated dosage administration is shown below. The tmax is naturally different for the two products. The 90% CI for the Cmin (mcg/ml) is also outside

the 80-125 % acceptable range, and is 26% lower for the XR product than the IR product. The Cmax was 17% lower in the XR group. The pivotal clinical trial (N01235) examined safety and efficacy of Keppra XR which used the final to-be marketed formulation of Keppra XR. According to the sponsor, Keppra XR was shown to be effective compared to placebo in this trial.

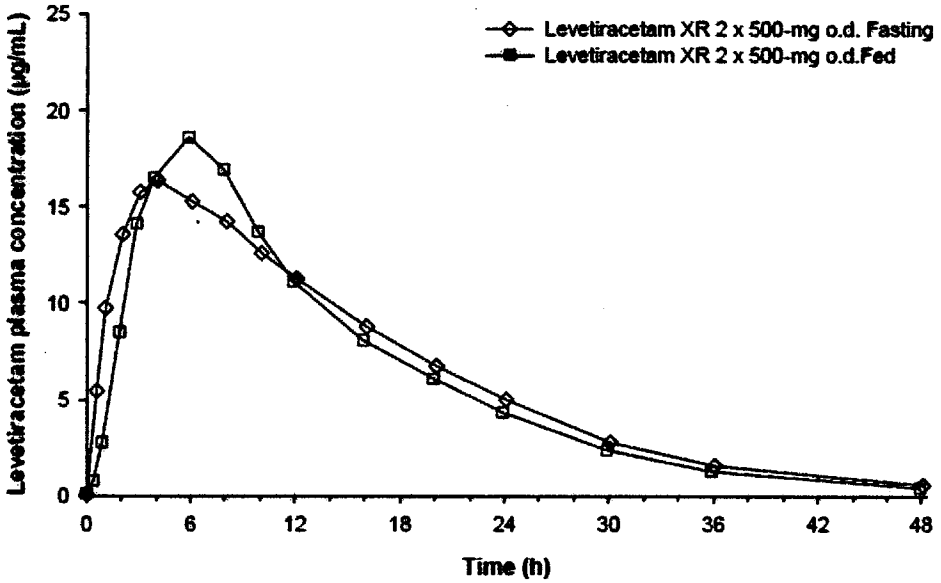
Table 2:12 **Bioequivalence Test between IR and XR Formulation under Fasting Conditions on Day 9 after Repeated Administration – N01160 PP Population**

| Parameter | CV[a] (%) | XR vs. IR Formulation[b] | |
|---|---|---|---|
| | | Point Estimate | 90% CI |
| $C_{max}$ (µg/mL) | 10.4 | 83.34 | (79.13 ; 87.76) |
| $t_{max}$ (h) | NC | 2.88 | (2.38 ; 3.25) |
| $AUC_{(0-24)}$ (µg.h/mL) | 4.39 | 94.16 | (92.08 ; 96.29) |
| MRTotal (h) | 16.9 | 94.07 | (86.38 ; 102.45) |
| Cmin (µg/mL) | 10.5 | 73.55 | (69.74 ; 77.57) |
| $T50\%C_{max}$ (h) | 18.4 | 2.45 | (1.21 ; 3.69) |
| $T75\%C_{max}$ (h) | 38.5 | 4.38 | (3.33 ; 5.43) |

(a) Intra-subject coefficient of variation
(b) Estimates are the ratio XR formulation/IR formulation (%) of geometric least squares means and 90% CI derived from ANOVA except $t_{50\%}$Cmax and $t_{75\%}$Cmax: estimates and 90% CI of the difference (h) XR-IR formulation of least squares means, and $t_{max}$: median and 90% nonparametric CI of the difference (h) XR-IR formulation
NC: Not calculated

**2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

High fat meal did not affect the AUC and Cmax for Keppra XR (90% confidence intervals were within 80-125%). Tmax was slightly prolonged (2 hours) in the fed state. Keppra XR can be taken with or without food.




PK parameters derived from the individual concentration profiles are summarized below:

| Parameter | Fasting[a] | Fed[a] | CV[b] (%) | XR - fed vs. fasting[c] | |
|---|---|---|---|---|---|
| | | | | Point Estimate | 90% CI |
| $C_{max}$ (µg/mL) | 17.4 (17.9) | 19.5 (20.9) | 12.9 | 112.04 | (105.29 ; 119.22) |
| $t_{max}$ (h) | 4.00 (2.00-10.00) | 6.00 (3.00-8.00) | NC | 2.50 | (2.00 ; 3.50) |
| AUC(0-t) (µg.h/mL) | 307 (15.1) | 293 (16.2) | 7.49 | 95.43 | (92.03 ; 98.96) |
| AUC (µg.h/mL) | 313 (15.1) | 298 (16.1) | 7.57 | 95.05 | (91.63 ; 98.60) |
| $t_{½}$ (h) | 7.60 (10.0) | 7.34 (12.1) | NC | NC | NC |

[a] Geometric means (CV%) and median (range) for $t_{max}$
[b] Intra-subject coefficient of variation
[c] Estimates are the ratio fed condition/fasting condition (%) of geometric least squares means and 90% CI derived from ANOVA except $t_{max}$: median and 90% nonparametric CI of the difference (h) fed-fasting condition
NC: Not calculated

## *2.6 Analytical section*

### 2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

A HPLC/UV assay has been developed to determine levetiracetam in plasma samples over the range of 1.0 to 80 µg/mL.

### 2.6.2 Which metabolites have been selected for analysis and why?

The major metabolite of Keppra in considered to be inactive and was not measured.

### 2.6.3 What bioanalytical methods are used to assess concentrations?

Gas and high pressure liquid chromatography

### 2.6.3.1 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The assay validation was adequate (see Table below).

Table 1: Bioanalytical Method Performance Summary

| Bioanalytical Method Performance Summary | | | |
|---|---|---|---|
| Lower Limit of Quantitation | 1.0 mcg/mL | | |
| Upper Limit of Quantitation | 80.0 mcg/mL | | |
| Inter-Assay Performance | Target = 5 mcg/mL | Target = 25 mcg/mL | Target = 65 mcg/mL |
| Precision (RSD) | 6.5 % | 9.4 % | 4.9 % |
| Accuracy (% of target) | 97 % | 99 % | 101 % |
| Stability | | | |
| Room Temperature | Stable for a minimum of 9 days. | | |
| Refrigerated (2°C) | Stable for a minimum of 23 days. | | |
| Frozen (-20°C) | Stable for up to 4 months. | | |
| Analyte Specificity | A wide variety of drugs encountered in human serum, plasma and blood, including other anticonvulsant drugs, commonly used non-narcotic analgesics, antihistamines and stimulant drugs have been excluded as interferences with this analysis. | | |
| Matrix Specificity | No significant interferences have been observed in human serum, plasma, and blood specimens. | | |

### 2.6.3.2 What is the QC sample plan?

Plasma samples are spiked with internal standard [redacted] and methanol for protein precipitation. Spiked samples are mixed, stored at -20 °C for 30 minutes, and centrifuged. The clear supernatant is injected in a gas chromatograph coupled with an NP detector and an FFAP column. b(4)

The linearity of the assay was assessed from peak height ratios (analyte/IS) as a function of analyte concentration after linear regression (least squares method with 1/x2 weighting). Quality control standards were prepared at low (4 µg/mL), middle (12.0 µg/mL), and high (20.0 µg/mL) concentrations.

The levetiracetam assay was linear in the measured concentration range of 0.5 to 40.0 µg/mL of plasma. The lower (LLOQ) and upper (ULOQ) limits of quantitation were respectively set to the lowest and highest concentration of the calibration range (0.5 and 40.0 µg/mL), as precision and accuracy acceptance criteria were fulfilled. The limit of detection, based on a signal-to-noise ratio of 3, was approximately 0.3

µg/mL for levetiracetam in plasma. The assay had acceptable precision and accuracy.

Table 2:2 **Validation Results for Levetiracetam Assay in Plasma**

| Validation Parameter | Results |
|---|---|
| Linearity | $r \geq 0.9936$ |
| Calibration curve range | 0.5 – 40.0 µg/mL |
| Lower limit of detection | 0.3 µg/mL |
| Lower limit of quantitation | 0.5 µg/mL |
| Within-run Precision (RSD%) | ≤ 2.6% |
| Between-run Precision (RSD%) | ≤ 2.4% |
| Total Precision (RSD%) | ≤ 3.5% |
| Total Accuracy | ≤ \| 3.1 \| |
| Recovery of Analyte | QC mean, low, medium, & high: 95.0, 96.4, and 95.5% |

Levetiracetam in plasma samples was found to be stable after three freeze/thaw cycles following a storage period of 3 days at room **temperature and 18 months at –20 °C**. The stability of levetiracetam and internal standard in stock solution during a 14-month period at **approximately –20 and 4 °C was cons**idered satisfactory. Extracted samples of levetiracetam and internal standard were found to be stable after a storage period of 96 hours on autoinjector trays at room **temperature and after 72 hours at about –20 °C.**

The detection and quantification of levetiracetam in plasma specimens from study N01235 was performed by [redacted] using a validated high performance liquid chromatography (HPLC). In summary, a 0.10 mL aliquot of specimen had an internal standard added [redacted], and was made basic. The samples were extracted with an organic solvent that was evaporated to dryness, followed by reconstitution with mobile phase. The reconstituted extractions were analyzed by HPLC with UV detection. Each analytical batch was independently calibrated using a linear curve fit using a 1/x weighting with calibration points of 1.0, 2.0, 10.0, 40.0 and 80.0 µg levetiracetam/mL bovine serum. Two levels of controls were run in each batch at nominal concentrations of 5.0 and 65.0 mcg levetiracetam mL bovine serum. b(4)

This assay was run in a clinical laboratory in compliance with CLIA, and was not conducted in a GLP compliant environment.

Table 2:3 **Performance Summary for Levetiracetam Assay in Plasma using the HPLC Method** [redacted] b(4)

| Validation Parameter | Results |
|---|---|
| Calibration curve range | 1.0 to 80.0 µg/mL |
| Lower limit of quantitation | 1.0 µg/mL |
| Precision (RSD%) | 4.9% - 9.4% |
| Total Accuracy | 97% - 101% |

# 24 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__✓__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Clin Pharm/Bio-* 5

## 4 Appendices

4.1 Package insert (see Section 3)

## 4.2 Clinical pharmacology and biopharmaceutics individual study review

**The extended release dosage form (Keppra XR) considered in this application is a 500 mg. tablet. The development program for this extended release dosage form has consisted of 5 studies with Keppra XR, four of which are in healthy subjects and one of which was in patients. One additional analysis and simulation was also conducted using all of the patients and healthy subjects who had received Keppra XR from the 5 studies.**

Table 2:2 Clinical Studies Included in NDA 22-285 for Levetiracetam Extended Release Tablet 500 mg

| Study No. | No. Randomized (Exposed to XR) | Dates of Conduct / Countries | Overview of Design |
|---|---|---|---|
| N01235 | 158 (77) | 21-Aug-2006 – 30-May-2007 / Brazil, Finland, India, Mexico, Russian Federation, South Africa, Ukraine | Double-blind, placebo-controlled, randomized, 1000 mg once daily, as add-on therapy in patients 12 – 70 years of age with refractory epilepsy with POS; 8-week baseline followed by 12 weeks of treatment. |
| N01173 | 9 (0) | 03-Jun-2004 – 28-Jul-2004 / United Kingdom (UK) | Single dose, 4-way crossover of LEV IR oral tablet 250 mg; LEV 250 (drug substance) delivered to proximal small bowel via [redacted] capsule; LEV 250 mg (drug substance) delivered to distal small bowel via [redacted] capsule; LEV 250 mg (drug substance) delivered to ascending colon via [redacted] capsule in healthy male volunteers (18 to 65 years, inclusive). b(4) |
| N01140 | 12 (12) | 16-Mar-2005 – 25-May-2005 / France | Single dose, open-label pilot study to compare the pharmacokinetics of LEV 500 mg from 3 XR test formulations with the IR reference formulation in healthy volunteers and to assess the influence of food on one of the test formulations (pilot bioequivalence study). |
| N01160 | 24 (24) | 04-Jul-2006 – 02-Sep-2006 / France | Randomized, open-label, three-way crossover study of LEV XR (1000 mg, once daily) and LEV IR (500 mg B.I.D.). Single and multiple dose bioequivalence and assessment of food effect on LEV XR in healthy volunteers. |
| N01260 | 24 (24) | 05-Jan-2007 – 26-Feb-2007 / France | Randomized, open-label, single dose, three-way crossover dose proportionality study of LEV XR 1000 mg, 2000 mg, and 3000 mg, in healthy volunteers. |

**The first study was N01173, and examined the absorption of levetiracetam from various portions of the gut to see if an extended release product was feasible.**

**Title of Study N01173:**
Pharmacoscintigraphic investigation of the regional absorption of levetiracetam (250 mg) delivered using the [redacted] capsule in 3 b(4)

different sites of the GI tract in comparison with the IR 250 mg oral tablet: open label, randomized, four-way cross-over study, in 9 healthy-adult male volunteers.

**Objectives:**
Primary: To determine the regional absorption profile of levetiracetam 250 mg from three different regions of the gastrointestinal tract (proximal small bowel, distal small bowel and ascending colon) using the [redacted] capsule drug delivery system compared with the 250 mg IR tablet absorption profile. b(4)
Secondary: To gain additional information about the safety of levetiracetam.

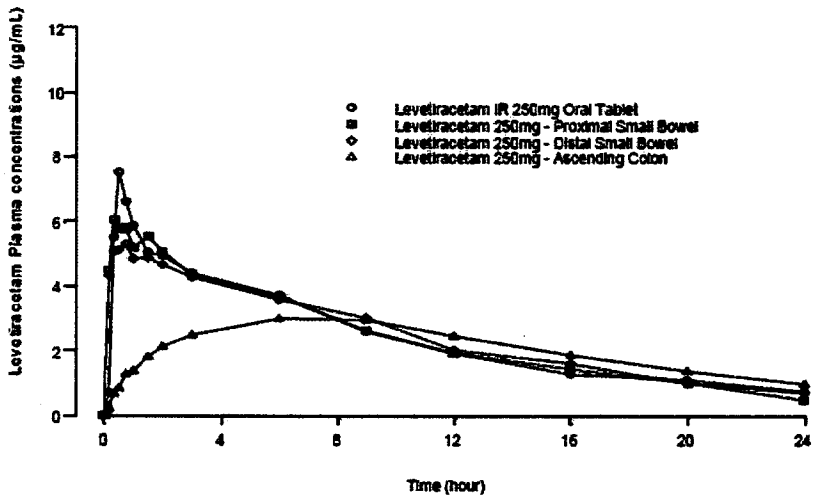
**Methodology:**
Pharmacoscintigraphic, randomized, open label, four-way crossover, oral, single dose administration in up to 9 healthy male volunteers.

**Pharmacokinetics:**
The pharmacokinetic parameters were: Cmax, tmax, AUC(0-t), AUC, t1/2, CL/F, Vz/F and Frel. Plasma samples were taken at the following time points: pre-dose, 10 min, 20 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 6 h, 9 h, 12 h, 16 h, 20 h and 24 h post-dose/activation.

**Scintigraphy:**
The scintigraphic data were analyzed to obtain the following parameters: gastric emptying time, small intestinal transit time, ileo-caecal junction (ICJ) arrival time, residence time in ICJ, colon arrival time, colon transit time, total transit time, anatomical location and time of successful [redacted] activation. b(4)

**Safety:**
General tolerability of each treatment assessed through adverse events, vital signs, physical examination,
ECG and laboratory results.

**Results:**




| Dose and Route of Administration | Statistic [a] | Summary Pharmacokinetic Parameters (n=6) | | | | |
|---|---|---|---|---|---|---|
| | | $C_{max}$ (µg/mL) | $t_{max}$ (h) | AUC(0-t) (µg*h/mL) | AUC (µg*h/mL) | $t_{1/2}$ (h) |
| IR 250 mg Oral Tablet | Geometric mean | 8.44 | 0.500 | 58.96 | 66.64[b] | 7.64[b] |
| | Range | 6.15-10.5 | 0.333-0.750 | 53.2-65.8 | 61.2-72.2 | 6.82-8.30 |
| 250 mg Proximal Small Bowel | Geometric mean | 6.77 | 0.350 | 58.22 | 66.55 | 7.73 |
| | Range | 5.79- 8.55 | 0.163-1.50 | 53.2-67.2 | 60.0-79.8 | 6.72-8.86 |
| 250 mg Distal Small Bowel | Geometric mean | 6.69 | 0.668 | 59.63 | 67.82 | 7.63 |
| | Range | 3.68-9.68 | 0.163-3.00 | 53.1-68.3 | 60.3-76.4 | 5.75-9.21 |
| 250 mg Ascending Colon | Geometric mean | 3.37 | 7.497 | 51.49 | 59.91[c] | 7.49[c] |
| | Range | 2.70-3.97 | 2.17-9.00 | 45.5-61.4 | 54.1-63.2 | 7.08-7.91 |

[a] for $t_{max}$, median is reported instead of geometric mean.
[b] n=5
[c] n=3

| Site of Administration | % Bioavailability(geometric mean ratio and 95% confidence intervals) [a] Relative to IR 250 mg Oral Administration | |
|---|---|---|
| | AUC | $C_{max}$ |
| Proximal Small Bowel | 98.51 (89.69 – 108.20) | 82.30 (68.00 – 99.59) |
| Distal Small Bowel | 100.79 (91.14 – 111.14) | 79.62 (65.41 – 96.93) |
| Ascending Colon | 87.14 (77.87 – 97.52) | 41.06 (33.72 – 50.00) |

[a] ) Geometric mean ratios and intervals were calculated using AUC values for Proximal and Distal Small Bowel, and AUC(0-t) values for Ascending Colon.

## Analysis:

This study was designed to find out whether LEV was absorbed over a broad enough area of the gut that it could accommodate the formulation of an extended release dosage form. If LEV absorption was restricted to one finite area of the gut, the concept of using an extended release dosage form would not work.

In this study, LEV was absorbed well from the proximal and distal small bowel, and adequately absorbed (87%) from the ascending colon.

Therefore the outcome was considered positive and the development program moved to the product formulation stage.

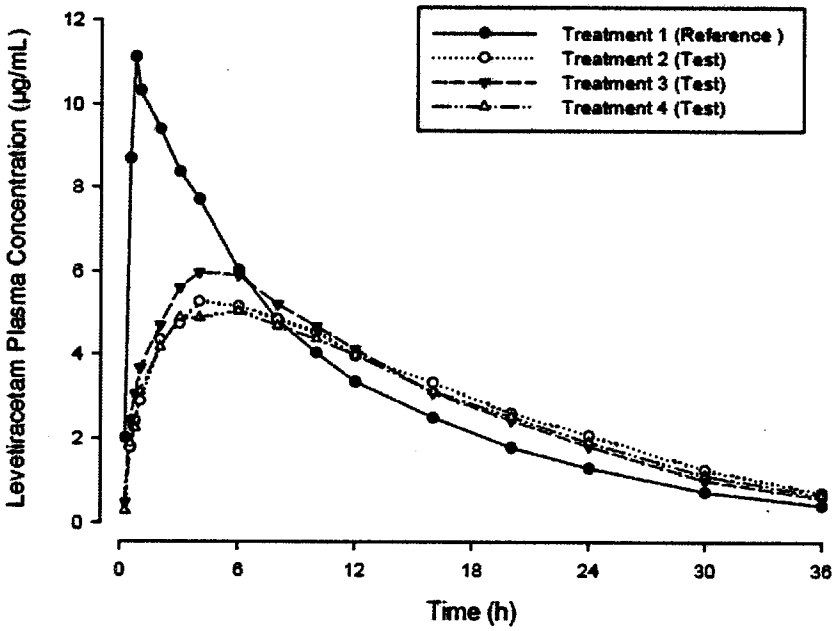
**The second study was NO1140, which tested three formulations of extended release tablets in 12 healthy subjects.**

**Title of Study NO1140:**
A single dose open-label pilot study to compare the pharmacokinetics of levetiracetam 500 mg oral dose from three extended release test formulations with the immediate release reference formulation in 12 healthy male volunteers and to assess the influence of food on one of the test formulations.

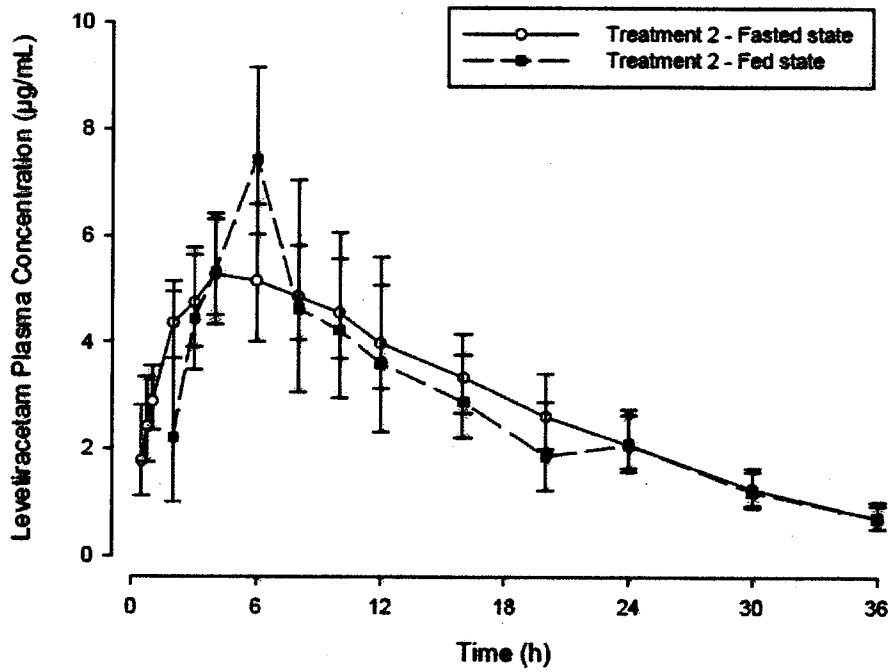
**Objectives:**
The primary objectives of the present study were to compare the pharmacokinetic profile of levetiracetam from each test formulation with the reference formulation and to gain an initial assessment of the influence of food on the selected test formulation.
The secondary objective was to gain information on the safety of levetiracetam test formulations.

**Methodology:**
This study was conducted as follows:
Study Periods 1-4: randomized, open label, four-way cross-over, single oral doses. Subjects were randomly administered in the fasted state one 500 mg levetiracetam IR tablet (reference, Treatment 1) or one 500 mg of one of three extended release formulations (test, Treatments 2, 3, 4), using a Latin-square design.
Study Period 5: Open, non-randomized, single oral dose. The same subjects received, 30 minutes after a high fat breakfast, 500 mg of one of the three extended release formulations administered in periods 1 to 4. The selection of the extended release formulation to administer in period 5 was to be based upon the PK parameters, tolerability results derived from periods 1 to 4. Each dose was separated from the next dose by a washout of 7 days. Study Periods 4 and 5 were separated by a wash-out of 21 days.

**Results:**




One formulation was tested fasting and with food, with the following result:




The adverse effects detected were mild to moderate in all cases, and no **SAE's were noted.**

**Analysis:**

This study dealt with the selection of a long acting formulation. All three formulations tested were similar. A fed and fasting study was reported with one of the products.

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**The third study was a dose proportionality study, study NO1260.**

**Title of Study:**
A randomized, monocenter, open-label, three-way cross-over dose proportionality study of oral levetiracetam in 24 healthy male and female volunteers.

**Objectives:**
*Primary:*
• **to compare the single dose bioavailability** of levetiracetam 2 x, 4 x, and 6 x 500 mg XR tablets.
*Secondary:*
• **to gain additional information on the sa**fety of levetiracetam XR tablets.

**Methodology:**
Monocenter, randomized, open-label, 3-way cross-over study.

**Dose and Mode of Administration:**
Single dose of oral XR tablets under fasting conditions
• **treatment 1: 2 x 500 mg**
• **treatment 2: 4 x 500 mg**
• **treatment 3: 6 x 500 mg**

**Assay Performance:**

Levetiracetam was measured in plasma by a validated LC-ESI/MS/MS assay using [redacted] as internal standard. The method has a lower limit of quantification of 0.100 µg/mL for Levetiracetam. Calibration measurements together with QC data in citrated human plasma were obtained from each run. b(4)

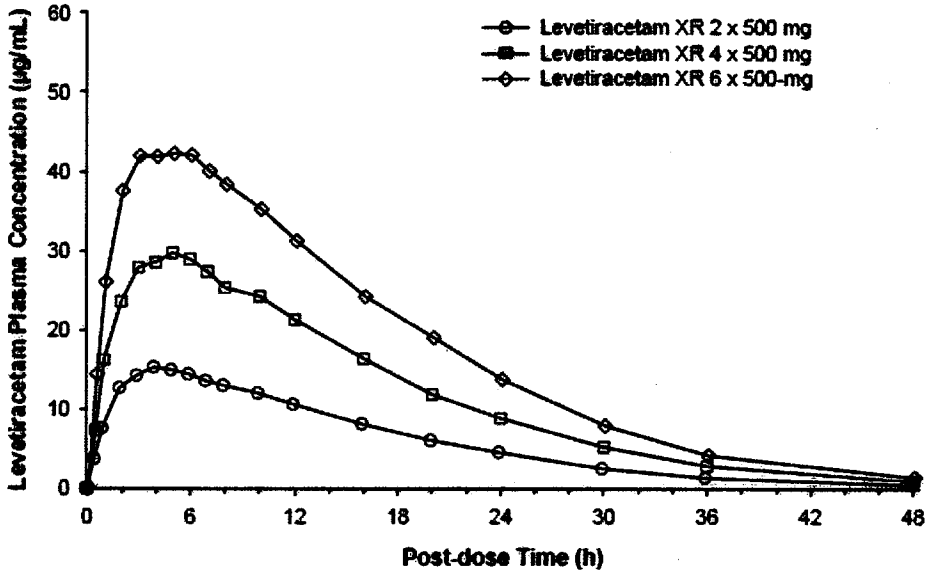
The means of relative deviations of Levetiracetam in QC samples were 2.0, 3.2 and -3.9% at nominal concentrations of 0.300, 25.0 and 80.0 µg/mL, respectively. For the 32 calibration curves, the $r^2$ was $\geq$0.9918 and the Y-intercept was 0.00199. For all runs of Quality Control samples, the CV was 8.7% at 80 mcg/ml, 9.6% at 25 mcg/ml, and 11.1% at 0.3 mcg/ml.

**Results:**

For the doses of 1000 mg, 2000 mg, and 3000 mg Keppra XR, the 90% CI of the slope was entirely in the dose-proportionality limits for the rate

(Cmax) and the extent of absorption (AUC) and in the dose-independent limits for half-life, apparent clearance, and apparent volume of distribution.

A total of 40 treatment-emergent AEs (TEAEs) were experienced by 18 subjects: 10 AEs reported by 5 subjects after 1 g levetiracetam XR, 12 AEs reported by 11 subjects after 2 g levetiracetam XR and 18 AEs reported by 13 subjects after 3 g levetiracetam XR. The most frequently reported TEAEs were: somnolence (9 subjects), asthenia (7 subjects), dizziness (4 subjects), muscle spasms (3 subjects), and rhinitis (3 subjects). All reported AEs were mild to moderate in intensity. None of the reported AEs led to treatment discontinuation. No SAEs were reported.




PK parameters derived from the individual concentration profiles are summarized below:

| Parameter (N=24) | Levetiracetam XR dose | | | Slope of the regression[b] | |
|---|---|---|---|---|---|
| | 2 x 500 mg[a] | 4 x 500 mg[a] | 6 x 500 mg[a] | Point Estimate | 90% CI |
| $C_{max}$ (µg/mL) | 16.2 (20.7) | 31.5 (18.8) | 46.2 (20.6) | 0.953 | (0.907 ; 0.999) |
| $t_{max}$ (h) | 4.50 (2.00-8.00) | 5.00 (2.00-10.00) | 4.50 (2.00-10.00) | NC | NC |
| AUC(0-t) (µg.h/mL) | 280 (17.6) | 559 (17.0) | 839 (15.9) | 0.998 | (0.973 ; 1.02) |
| AUC (µg.h/mL) | 285 (17.6) | 570 (17.1) | 855 (16.1) | 0.998 | (0.973 ; 1.02) |
| $t_{½}$ (h) | 7.26 (12.1) | 7.33 (14.1) | 7.15 (13.1) | -0.0120 | (-0.0443 ; 0.0202) |
| CL/F (mL/min) | 58.4 (17.6) | 58.5 (17.1) | 58.5 (16.1) | 0.00174 | (-0.0234 ; 0.0268) |
| $V_z$/F (L) | 36.7 (22.0) | 37.1 (21.3) | 36.2 (18.0) | -0.0103 | (-0.0504 ; 0.0298) |

[a] Geometric means (geometric CV%) and median (range) for $t_{max}$
[b] Linear regression between log-transformed parameter and log-transformed dose
NC: not calculated

## Analysis:

The BE Guidance states that the food and fasting study be conducted with the highest dosage strength. The 500 mg Keppra XR is the only dosage strength in this application. Although larger doses have been used clinically, the 1000-3000 mg dosage range is the labeled adult dosage for Keppra XR. Therefore it appears that absorption is dose proportional for this product.

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**The fourth study (NO1160) was a pivotal randomized three way crossover study in 24 healthy subjects of Keppra immediate release 500 mg tablets versus Keppra XR 1000 mg (two 500 mg tablets) administered as a single dose and as multiple doses while fasting, along with a study after a meal.**

**Title of Study:**
A randomized, monocenter, open-label, three-way cross-over study of oral levetiracetam 2 x 500 mg extended release (XR) *o.d.* formulation and 500 mg immediate release (IR) *b.i.d.* formulation: single and multiple dose bioequivalence and assessment of the food effect on the XR formulation in 24 healthy male and female volunteers.

**Objectives:**
*Primary*:
• **to compare the single dose bioavailab**ility of levetiracetam 2 x 500 mg XR formulation *o.d.* with levetiracetam 500 mg IR oral tablet administered twice on Day 1;
• **to compare the multiple dose bioava**ilability of levetiracetam 2 x 500 mg XR formulation *o.d.* with levetiracetam 500 mg IR oral tablet b.i.d;
• **to assess the food effect** on the levetiracetam 2 x 500 mg *o.d.* XR formulation;
*Secondary*.
• **to gain additional information on the** safety of both levetiracetam formulations.

**Methodology:**
Monocenter, randomized, open label, 3-way cross-over study.

**Dose and Mode of Administration:**
2 x 500 mg oral XR tablets
• **treatment 2: single dose under** fasting conditions on Day 1 followed by a repeated administration *o.d.* from Day 3 to Day 9
•**For all regimens under fasting conditi**ons, the subjects were fasted from 10 pm the evening preceding each morning administration and until 4 h after the study drug intake. For the treatment 3, the subjects were fasted from 10 pm the evening preceding administration to 30 min pre-dose, when they were served a high-fat, high-calorie breakfast. This breakfast included two buttered toasts, two eggs fried in butter, two slices of bacon,

120 g hash brown potatoes, and 240 mL of whole milk, which contains approximately 150 protein calories, 250 carbohydrate calories and 500 to 600 fat calories.

**Subject Demographics:**
Twenty-one subjects were Caucasian (10 men and 11 women), 2 men were Black, and 1 woman was from another ethnic origin. Fifteen subjects consumed caffeinated beverages (at most 4 cups a day). All subjects were non-smokers, including six subjects having stopped smoking at least 6 months before the trial. Two subjects moderately consumed alcohol (at most 7 units a week). None of the subjects reported history of illicit drug use. Other information is provided in the Table below:

**Table 11:1 Demographic Data – ITT Population (N=24)**

| Parameter | Mean | SD | Median | Minimum | Maximum |
|---|---|---|---|---|---|
| Age (years) | 30.8 | 10.3 | 27.6 | 18.6 | 51.9 |
| Height (cm) | 168.8 | 8.0 | 169.5 | 154 | 181 |
| Weight (kg) | 66.3 | 7.7 | 68.3 | 51 | 79 |
| BMI (kg/m$^2$) | 23.3 | 2.4 | 23.2 | 19.2 | 27.7 |
| BSA (m$^2$) | 1.76 | 0.13 | 1.80 | 1.5 | 1.9 |

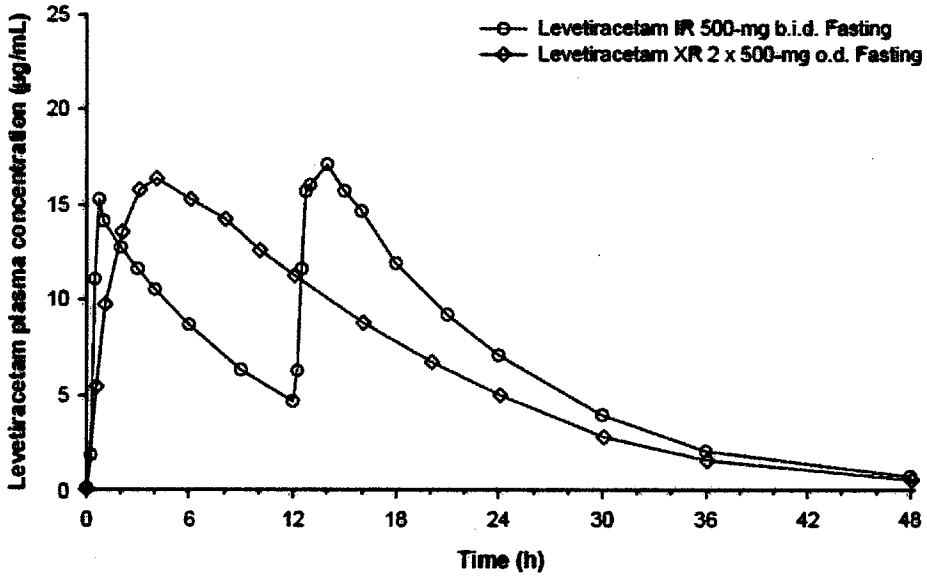
Source: Table 14.1.2:1

**Assay performance:**
Levetiracetam was measured in plasma by a validated LC-ESI/MS/MS assay using [redacted] as IS. The method has a lower limit of quantitation of 0.100 µg/mL for levetiracetam. Calibration measurements together with QC data in citrated human plasma were obtained from each run. The means of relative deviations of levetiracetam in QC samples were 3.0, 3.2 and -6.1% at nominal concentrations of 0.3, 25 and 80 µg/mL, respectively. For all quality control samples, the CV was 8.2% at 80 mcg/ml, 8.8% at 25 mcg/ml, and 9.9% at 0.3 mcg/ml.

b(4)

**Results:**

Food versus fasting: Time to peak was delayed by about 3 h after administration of XR tablets in comparison to the administration with IR tablets. No relevant difference in the other PK parameters was found: both treatments were bioequivalent (90% CIs of the treatment ratio of Cmax and AUCs were fully included in the interval [80%-125%]). Inter- and intra-subject variability was low (CV% generally below 20%).

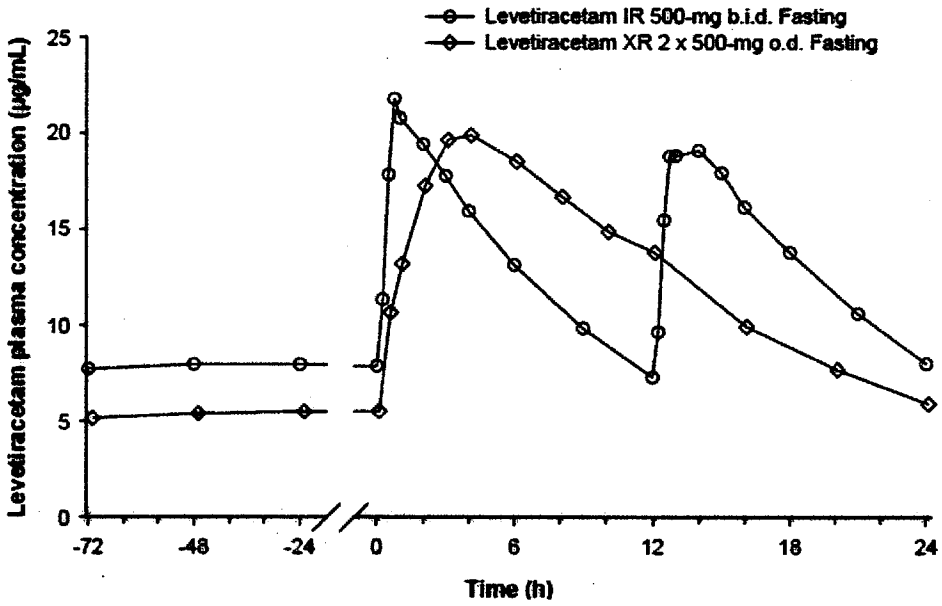



**PK parameters derived from the individual concentration profiles are summarized below:**

| Parameter | IR tablet[a] | XR tablet[a] | CV[b] (%) | XR vs. IR Formulation[c] | |
|---|---|---|---|---|---|
| | | | | Point Estimate | 90% CI |
| $C_{max}$ (µg/mL) | 19.7 (17.1) | 17.4 (17.9) | 12.9 | 88.49 | (83.16 ; 94.17) |
| $t_{max}$ (h)[d] | 0.88 (0.50-3.03) | 4.00 (2.00-10.00) | NC | 2.88 | (2.25 ; 3.25) |
| AUC(0-t) (µg.h/mL) | 317 (13.9) | 307 (15.1) | 7.49 | 96.71 | (93.26; 100.28) |
| AUC (µg.h/mL) | 325 (13.8) | 313 (15.1) | 7.57 | 96.31 | (92.84 ; 99.91) |
| $t_{½}$ (h) | 7.28 (12.1) | 7.60 (10.0) | NC | NC | NC |

[a] Geometric means (CV%) and median (range) for $t_{max}$

Multiple dose administration:



PK parameters derived from the individual concentration profiles are summarized below:

| Parameter | IR tablet[a] | XR tablet[a] | CV[b] (%) | XR vs. IR Formulation[c] | |
|---|---|---|---|---|---|
| | | | | Point Estimate | 90% CI |
| $C_{max}$ (µg/mL) | 25.6 (18.6) | 21.3 (14.2) | 10.4 | 83.34 | (79.13 ; 87.76) |
| $t_{max}$ (h)[d] | 0.75 (0.25-2.00) | 4.00 (2.00-6.00) | NC | 2.88 | (2.38 ; 3.25) |
| AUC(0-24) (µg.h/mL) | 327 (15.9)[e] | 309 (13.3) | 4.39 | 94.16 | (92.08 ; 96.29) |
| $C_{av}$ (µg/mL) | 13.6 (15.8)[e] | 12.9 (13.3) | NC | NC | NC |
| PTF (-) | 1.27 (21.5)[e] | 1.19 (11.7) | NC | NC | NC |
| $MRT_{oral}$ (h) | 10.6 (25.2)[e] | 10.1 (23.1) | 16.9 | 94.07 | (86.38; 102.45) |
| $C_{min}$ (µg/mL) | 8.02 (21.9)[e] | 5.93 (17.2) | 10.5 | 73.55 | (69.74 ; 77.57) |
| $T_{50\%Cmax}$ (h) | 12.4 (26.3) | 14.8 (14.0) | 18.4 | 2.45 | (1.21 ; 3.69) |
| $T_{75\%Cmax}$ (h) | 3.41 (67.1) | 7.79 (27.1) | 38.5 | 4.38 | (3.33 ; 5.43) |

[a] Geometric means (CV%), median (range) for $t_{max}$, and arithmetic means (CV%) for $T_{50\%Cmax}$ and $T_{75\%Cmax}$
[b] Intra-subject coefficient of variation
[c] Estimates are the ratio XR formulation/IR formulation (%) of geometric least squares means and 90% CI derived from ANOVA except $T_{50\%Cmax}$ and $T_{75\%Cmax}$: estimates and 90% CI of the difference (h) XR-IR formulation of least squares means, and $t_{max}$: median and 90% nonparametric CI of the difference (h) XR-IR formulation
[d] $t_{max}$ is the time from the latest administration before $C_{max}$
[e] N=23 (Subject 0022 had 2 missing samples at the end of the profile)
NC: Not calculated

After repeated dosing over one week, extent of exposure (AUC) after two 500-mg levetiracetam XR tablets *o.d* was equivalent to one 500-mg levetiracetam IR tablet *b.i.d*, the lower 90% CI limit of the Cmax ratio (XR/IR) was marginally below the 80% - 125% bioequivalence range (79.13%). The Cmin was approximately 26% lower for Keppra XR.

**Analysis:**
This was the pivotal BE study relating both to food versus fasting and for multiple dose administration in 24 healthy subjects. The Keppra XR product showed similar exposure (with a lower Cmin) compared to the immediate release product when given as a 1000 mg dose for the XR product versus immediate release 500 mg [redacted] Food did not have a significant effect upon LEV Cmax or AUC. On chronic administration, LEV Cmin was lower with the Keppra XR product than with the Keppra IR product.

b(4)

**The fifth study was a double blind, randomized placebo-controlled study of 1000 mg/day in 158 seizure patients of 12-70 years old examining efficacy and safety.**

**Title of Study:**
A double-blind, placebo-controlled, randomized efficacy and safety study of levetiracetam extended release formulation (LEV XR), administered as 2x500 mg LEV XR tablets once daily as add-on therapy in subjects from 12 to 70 years with refractory epilepsy suffering from partial onset seizures.

**Objectives:**
The primary objective was to evaluate the efficacy of LEV XR 2x500 mg/day, once daily as adjunctive therapy in the treatment of refractory epilepsy patients 12 to 70 years of age with partial onset seizures in comparison with placebo. The secondary objective was to evaluate the safety and tolerability of LEV XR 2x500 mg/day, once daily as adjunctive therapy in the treatment of refractory epilepsy patients 12 to 70 years of age with partial onset seizures.

**Methods:**

**Diagnosis and Main Criteria for Inclusion:**
• **Male/female subjects, 12 to 70 years** of age inclusive, suffering from partial onset seizures according to the ILAE classification of epileptic seizures, whether or not secondarily generalized.
• **Subjects with diagnosed** epilepsy for a minimum of 6 months prior to the Selection Visit (Visit 1).
• **Presence of the following during the** eight weeks of the Baseline Period: at least eight partial seizures (Type IA, IB, or IC) with or without secondary generalization and at least two partial seizures in each 4-week interval of the Baseline Period.
• **Subjects on a stable dose for at** least four weeks before the Selection Visit of at least one and no more than three other concomitant antiepileptic drugs (AEDs). Benzodiazepines were considered as an AED if taken at a frequency greater than an average of once/week, whatever the indication.

**Duration of Treatment:**
The study duration per subject was approximately 22 weeks: an 8-week Baseline Period followed by a 12- week Treatment Period with a Final Visit occurring within the two weeks after the last investigational drug intake for the subjects discontinuing prematurely or deciding to not convert to LEV IR (Immediate Release).

**Criteria for Evaluation:**
**Efficacy:**
The primary efficacy variable was as follows:
• **The partial onset seizure (Type** I) frequency per week over the Treatment Period.
**The secondary efficacy variables were as follows:**
• **The total seizure (Type I + II** + III) frequency per week over the Treatment Period.
• **The absolute and percentage (%) reduction** from baseline in partial onset seizure (Type I) frequency per week over the Treatment Period.
• **The absolute and percentage (%) reduction** from baseline in total seizure (Type I + II + III) frequency per week over the Treatment Period.

• **The responder rate (the proportion of subjects who have a ≥** 50% reduction in seizure frequency per week from baseline) for partial onset seizures (Type I) and for total seizures (Type I + II + III) over the treatment Period.
• **The categorical response to treatm**ent: percent reduction from baseline in partial onset seizure (Type I) and in total seizure (Type I + II + III) frequency per week grouped into six categories (< -25%, -25% to < 25%, 25% to < 50%, 50% to < 75%, 75% to < 100% and 100%) over the Treatment Period.

In this clinical study, 77 patients were exposed to Keppra XR over a twelve week period and had trough plasma concentrations of levetiracetam measured.

**Results:**

**EFFICACY RESULTS (primary variable):**
The primary efficacy analysis was carried out on both the ITT and the PP populations as there were more than 10% subjects with major protocol deviations. The median percent reductions in partial onset seizure (Type I) frequency per week over the Treatment Period from Baseline were 46.1% in LEV XR vs. 33.4% in PBO. The estimated percent reductions over PBO in partial onset seizure (Type I) frequency per week over the Treatment Period was 14.4% in the ITT population; this reduction over PBO was statistically significant at the 2-sided 5% significance level (p = 0.038).

The estimated percent reductions over PBO in partial onset seizure (Type I) frequency per week over the Treatment Period was 18.6% in the PP population; this reduction over PBO was statistically significant at the 2-sided 5% significance level (p = 0.003).

**SAFETY RESULTS:**
Safety analyses were carried out on the safety population (79 PBO; 77 LEV XR), excluding from the ITT population the 2 subjects who were randomized to LEV XR and were proven not to have taken any study drug. Two hundred forty-three treatment-emergent AEs (TEAEs) (125 in the PBO group; 118 in the LEV XR group) were reported. Overall, the incidence of the TEAEs reported in the two treatment groups was similar: there were 43 subjects (54.4%) in the PBO group and 41 subjects (53.2%) in the LEV XR group reporting at least one TEAE. The intensity of most of the TEAEs was mild to moderate.

Nine treatment-emergent SAEs, including the death, were reported by 8 subjects (2 [2.5%] in the PBO group and 6 [7.8%] in the LEV XR group). **The SAEs reported were (Preferred Term) 'stupor', 'partial seizures with**

**secondary generalization', 'epilepsy' in the PBO group and 'respiratory failure', 'epilepsy', 'rash', 'ischaemic stroke', 'simple partial seizures' and 'concussion' in the LEV XR group.** The majority of the SAEs resolved before the end of the study, **some with sequelae ('ischaemic stroke', 'concussion').**

**Analysis:**

As discussed in the review above, Keppra XR did meet the primary efficacy goals, and was more effective than placebo as adjunctive therapy in partial onset seizures.

Upon further analysis of the data from this study, only six patients 12-16 years of age were treated with Keppra XR. This not only creates too small a patient population for assurance that this dosage is appropriate for adolescents, but also the mean trough concentration was almost 80% higher than the mean trough concentrations in the adult patients treated with Keppra XR. This is the basis for approval only in adults, and for the need for additional future study in adolescents

b(4)

Looking at ethnic groups in this study, the Hispanic patients treated with Keppra XR had a 40% higher mean trough concentration than did the Caucasian patients. Since this ethnic group had not been studied with LEV previously, this may not be attributable to the XR formulation. However, given the number of Hispanic patients in the US requiring anticonvulsant therapy, and consideration should be given to review of dosing and safety information by the sponsor regarding Keppra use in the Hispanic patient population.

**One additional population PK study was done in the healthy subjects and patients who had been given Keppra XR in the studies above.**

**Title of Study:** Retrospective population pharmacokinetic analysis of levetiracetam extended-release in healthy and epileptic population

**Objectives**:
The main objectives of the analysis were to characterize the pharmacokinetics of levetiracetam administered as Extended Release (XR) formulation in healthy subjects and in epilepsy patients with partial onset seizures, to identify factors affecting pharmacokinetic parameters, and to simulate scenarios of non-compliance.

**Results:**

The typical first order absorption rate constant was about 20-fold lower for levetiracetam XR tablet than for IR tablet and was only slightly reduced by a high fat meal. The corresponding absorption half-times (ln(2)/Ka) were

0.1 h, 2 h and 2.3 h for levetiracetam IR, XR fasting, and XR fed, respectively. The apparent clearance and distribution volume for the typical individual, *viz.* 0.92 mL/min/kg and 0.6 L/kg, were consistent with previous knowledge of oral levetiracetam pharmacokinetics. Consistent with the known pharmacokinetics of oral levetiracetam, bodyweight affected clearance and volume by approximately [-20%;+50%] and [-10%;+20%] around the typical value, respectively, over the extreme weights of 50 kg and 120 kg. Clearance was approximately 15% lower in female and was modified by about 10% over the range of creatinine clearance (45 mL/min to 140 mL/min).

**Analysis:**

No new information was generated from this analysis, and the described difference in the Hispanic patients was not detected.

**4.3 Consult reviews - None**

## 4.4 Cover sheet and OCPB filing/review form

The standard OCPB filing/review form provides a line listing of all studies.

**Office of Clinical Pharmacology and Biopharmaceutics**
***New Drug Application Filing and Review Form***

**General Information About the Submission**

| | Information | | Information |
|---|---|---|---|
| NDA Number | 22-285 | Brand Name | Keppra XR |
| OCPB Division (I, II, III) | DCP-I | Generic Name | Levetiracetam |
| Medical Division | HFD-120 | Drug Class | Antiepileptic agent |
| OCPB Reviewer | Gilbert Burckart, Pharm.D. | Indication(s) | Adjunctive therapy in the treatment of partial onset seizures in adults and adolescents [redacted] years of age and older with epilepsy |
| OCPB Team Leader | Ramana S. Uppoor, PhD | Dosage Form | Extended release tablet, white, film-coated (500 mg) |
| | | Dosing Regimen | Treatment should be initiated with a dose of 1000 mg od. Dosage may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg. |
| Date of Submission | November 29, 2007 | Route of Administration | Oral |
| Estimated Due Date of OCPB Review | 7/27/2008 | Sponsor | UCB, Inc |
| PDUFA Due Date | 9/14/2008 | Priority Classification | S |
| Division Due Date | 8/13/2008 | | |

b(4)

## Clin. Pharm. And Biopharm. Information

**Summary:**

The sponsor submits this NDA seeking approval of levetiracetam extended release tablet (Keppra XL) 500 mg as adjunctive therapy in the treatment of partial onset seizures in adults and adolescents [redacted] years of age and older with epilepsy. Levetiracetam is currently supplied as IR oral, oblong film-coated tablets (Keppra®) and labeled for 1000-3000 mg daily in adults. b(4)

This NDA submission contains four Phase 1 clinical pharmacology studies (N00173, N01140, N1160, and N01260) and one Phase 3 pivotal efficacy and safety study (N01235), and is primarily supported by Studies N01160, N01260, and N01235. The clinical pharmacology program was designed to provide information pertaining to single- and multiple-dose BA/BE of Keppra XL 500 mg as compared to reference IR tablet of the same strength (N01160), the dose proportionality over the 1000-3000 mg dose range (N01260), and the food effect (N01160). The double-blind, placebo controlled clinical trial evaluated the efficacy and safety of a fixed 1000 mg XR od in patients ≥12 years of age, weighing ≥50 kg, with partial onset seizures and were already on stable doses of 1-3 concomitant AEDs (N01235). The primary endpoint was the partial seizure (Type I) frequency per week over the treatment period. During early drug development, relative BA of 3 different prototypes XL were tested against reference IR tablet (N01140). The clinical service formulation was essentially identical to the proposed commercial formulation used in each of these studies, except a different identifier used for the latter. Additional study was conducted to investigate the gastric regional absorption of levetiracetam 250 using [redacted] encapsulated formulation vs. IR tablet (N01173). Additional information is available in Appendix 1. b(4)

The dose- or exposure-response relationship is not available. A retrospective population PK analysis (N01286), including Monte Carlo simulations, was performed using the plasma data in healthy and epileptic population from studies N01160, N01260, and N01235 to identify factors that potentially affect PK parameters. A multimedia dissolution study was performed. Effect of alcohol on in vitro release profiles was investigated with 0.05M phosphate buffer at pH 6.0 containing 5%, 10%, 20%, and 40% alcohol (v/v).

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments if any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | | | | |
| **Tabular Listing of All Human Studies** | | | | |
| **HPK Summary** | | | | |
| **Labeling** | | | | • Annotated PDF file; Word file |
| **Reference Bioanalytical and Analytical Methods** | X | | [redacted] | • Validation report for clinical pharmacology studies (GC with NP detection by UCB Pharma, S.A.) is provided.<br>• Validation report for clinical study N01235 (HPLC with UV detection by NMS Lab) is not provided b(4) |
| **I. Clinical Pharmacology** | - | - | - | |
| **Mass balance:** | - | - | - | |
| **Isozyme characterization:** | - | - | - | |
| **Blood/plasma ratio:** | - | - | - | |
| **Plasma protein binding:** | | - | - | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| *Healthy Volunteers-* | | | | |
| single dose: | - | - | - | |
| multiple dose: | - | - | - | |
| Patients- | | | | |
| single dose: | - | - | - | |

| | | | | |
|---|---|---|---|---|
| multiple dose: | - | - | - | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | X | 1 | 1 | Study N01260:<br>- XR 2x500mg vs. 4x500mg vs. 6x500mg tablets |
| fasting / non-fasting multiple dose: | - | - | - | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | - | |
| In-vivo effects of primary drug: | X | | | |
| In-vitro: | - | | - | |
| **Subpopulation studies -** | | | | |
| ethnicity: | - | | - | |
| gender: | - | | - | |
| pediatrics: | - | | - | |
| geriatrics: | - | | - | |
| renal impairment: | - | | - | |
| hepatic impairment: | - | | - | |
| **PD:** | | | | |
| Phase 2: | X | | - | |
| Phase 3: | X | | - | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | X | | - | |
| Phase 3 clinical trial: | X | | - | |
| **Population Analyses -** | | | | |
| Data rich: | - | | - | |
| Data sparse: | X | 1 | 1 | N01286:<br>- Plasma data from N01160, N01260, and N01235 |
| **II. Biopharmaceutics** | | | - | |
| **Absolute bioavailability:** | - | | - | |
| **Relative bioavailability -** | | | | |
| solution as reference: | - | | - | |
| alternate formulation as reference: | - | | - | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | 3 | 3 | Study N01173:<br>- Single-dose<br>- Regional absorption profiles of 250-mg LEV [redacted] capsules vs. 250-mg LEV IR tablets)<br><br>Study N01140: (pilot BA/BE)<br>- Single-dose fasting<br>- 3 test XR formulations (500-mg) vs. IR 500-mg tablet<br><br>Study N01160: (pivotal BA/BE)<br>- Single-dose, fasting, XR 2x500mg od vs. IR 500mg bid<br>- Multiple-dose, fasting, XR 2x500mg od vs. IR 500mg bid |
| replicate design; single / multi dose: | - | | - | |
| **Food-drug interaction studies:** | | (2) | 2 | Study N01140: (pilot BA/BE)<br>- Single-dose, fed, 1 test XR formulations 500-mg<br><br>Study N01160: (pivotal BA/BE)<br>- Single-dose, XR 2x500mg after high-fat food |
| **Dissolution:** | | 1 | 1 | Alcohol effect |
| **(IVIVC):** | - | | - | |
| **Bio-waiver request based on BCS** | - | | - | |
| **BCS class** | | | - | |
| **III. Other CPB Studies** | | | | |

b(4)

| | | | | |
|---|---|---|---|---|
| Genotype/phenotype studies: | - | | - | |
| Chronopharmacokinetics | - | | - | |
| Pediatric development plan | - | | - | |
| Literature References | | 10 | - | |
| Total Number of Studies | | 6 | 6 | |
| | | | | |

Filability and QBR comments

| I. | "X" if yes | Comments |
|---|---|---|
| II. Application filable ? | | Reasons if the application is not filable (or an attachment if applicable)<br>For example, is clinical formulation the same as the to-be-marketed one? |
| III. Comments sent to firm ?<br>IV. | X | Comments have been sent to firm (or attachment included). FDA letter date if applicable.<br><br>Please forward to Sponsor:<br>1. Please provide the validation report for HPLC method used for plasma sample from clinical study N01235, analyzed by [redacted] laboratory. b(4) |
| QBR questions (key issues to be considered) | • Adequate characterization of single- and multiple-dose PK of levetiracetam from XL formulation<br>• Establishment of relative BA between XR 2x500mg od and IR 500mg bid<br>• Establishment of dose proportionality between 1000 mg and 3000 mg dose range<br>• Potential food effect on bioavailability of levetiracetam from XL formulation<br>• Sources of inter-subject variability based on retrospective population PK analysis<br>• PK in patients and healthy subjects<br>• Adequately and appropriately validated bioanalytical methods | |
| Other comments or information not included above | | |
| Primary reviewer Signature and Date | | |
| Secondary reviewer Signature and Date | | |

CC: NDA 22-285, HFD-850(Electronic Entry or Lee), HFD-120(S. Daugherty), HFD-860 (R. Uppoor, M. Mehta)

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/s/
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Gilbert J Burckart
9/5/2008 10:38:08 AM
UNKNOWN

Ramana S. Uppoor
9/5/2008 10:50:09 AM
BIOPHARMACEUTICS

Mehul Mehta
9/5/2008 11:48:50 AM
BIOPHARMACEUTICS