Clinical Pharmacology/Biopharmaceutics Review

NDAs	21872/S-016 and 22285/S-018
NDA type	Labeling Supplements to fulfill PREA PMR
Submission Dates	Sept 30, 2013 and Oct 3, 2013
Brand Name	Keppra injection and Keppra XR
Generic Name	Levetiracetam
Sponsor	UCB, Inc.
Reviewers	Hristina Dimova, PhD Xiaofeng Wang, Ph.D.
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OCP Division	Clinical Pharmacology 1 (DCP1)
OND Division	Division of Neurology Drug Products

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1.0 EXECUTIVE SUMMARY

Levetiracetam (LEV), an antiepileptic drug, was first approved in 1999 as Keppra®, an immediate release (IR) tablet, NDA 21035, and oral solution, NDA 21505, with the following indications: adjunctive therapy of partial onset seizures; adjunctive treatment of myoclonic seizures and primary generalized tonic-clonic seizures.
Keppra, 500 mg/5 mL (100 mg/mL) injection (LEV IV) was later approved in 2006 for the same indications as the IR tablet in patients ≥16 years of age with epilepsy. The following PMR was included in the NDA 21872 Approval Letter (July 31, 2006):
1. Deferred pediatric study under PREA for a pharmacokinetic and safety study in 30 pediatric patients ages four to 16 years.
Specific commitments for studies in patients ages one month to four years will be discussed at a later date.

An extended release tablet, Keppra XR®, was approved in 2008, indicated for adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. Treatment with levetiracetam in an extended-release form is initiated with a dose of 1000 mg once daily, and adjusted in increments of 1000 mg to a maximum recommended daily dose of 3000 mg. Although the pivotal study enrolled patients down to the age of 12, the small number of patients exposed to drug below the age of 16 (only 7), together with the observation that the pharmacokinetics of this formulation seemed to be different between these younger patients and adults (see Dr. Burckart's review; however, only trough levels were available), made it difficult to offer adequate dosing recommendations for patients below the age of 16.
The following PMR was included in the NDA 22-285 Approval Letter (Sept 12, 2008):
1. Conduct an open label, single dose, pharmacokinetic study with Keppra XR in patients with epilepsy, ages 12-16 years, in comparison to adult patients with epilepsy. The patient population can presently be receiving Keppra. The pharmacokinetic study would include at least 6 pharmacokinetic samples. The comparison group will be an equal number of adult patients studied under the same conditions.
For each group (adolescents and adults), the mean Cmax and AUC must be estimated with a standard error of 20% or less, and this would be the basis for the original sample size calculation. As study data are evaluated, the sample size can be re-assessed if necessary for precise estimation of these pharmacokinetic parameters.

The current submissions are Required Pediatric Assessments Prior Approval Labeling Supplements to fulfill the above PREA PMRs. The sponsor proposes to incorporate new pediatric PK, safety, & tolerability data in pediatric patients and update the dosing regimen for 12 to 16 years of age for Keppra XR and down to 1 month of age for Keppra injection.

The sponsor conducted two open-label, single-arm trials in 33 subjects between 4 and 16 years of age and in 19 subjects between 1 month and below 4 years of age, respectively, receiving levetiracetam 15-min intravenous infusions at doses between 7 mg/kg/day and 30 mg/kg/day twice daily. A population pharmacokinetic analysis for the intravenous

formulation demonstrated that LEV plasma concentrations and model derived steady-state exposure $AUC_{(0-12)}$ were within the range of the exposure observed in pediatric patients receiving equivalent doses of Keppra oral solution.

For Keppra XR, an open label, multicenter, parallel-group, two-arm study was conducted to compare the pharmacokinetics of Keppra XR in pediatric patients (aged 12-16 years old) with epilepsy and in adults (aged 18-55 years old) with epilepsy. Dose-normalized steady-state exposure parameters, C_{max} and AUC in the pediatric patients were comparable to those in adults.

1.1 RECOMMENDATION

The submissions are acceptable from a Clinical Pharmacology and Biopharmaceutics point of view provided the sponsor agrees with the Agency's labeling recommendations. The reviewer's labeling recommendations are shown by track changes to the sponsor proposed labels.

In addition, these submissions are considered to fulfill the PREA PMRs.

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The clinical pharmacology findings for Keppra IV are as follows:

- The pharmacokinetics of LEV was characterized in children aged from 1 month to 15.5 years inclusive after 15-minute IV infusions (Studies N01274 and N01275). A population PK analysis was performed using combined PK data obtained from N01274 and N01275. The only covariates explaining the variability were BW on both CL and V, followed by a factor based on age taking into account the renal maturation on CL. However, the maturation factor had a greater than 20% effect on the exposure parameters in the youngest age range only (between 1.5 and 5.5 months old).
- The data did not support (b) (4) in the model.
- The observed plasma concentrations in studies N01274 and N01275 were compared to those achieved after oral administration of Keppra olal tablets or solution (from a previous population PK study N01288, using data from 6 clinical studies); they were overall in the same range at similar doses per kg. Therefore, in pediatric patients, the dosing recommendations for Keppra IV should be the same as these for Keppra oral (IR or oral solution), and no dose adjustment is necessary when switching from one route of administration to the other.

The clinical pharmacology findings for Keppra XR are as follows:

- Keppra XR (individual, daily dose: 1000mg to 3000mg) was administered for 4 to 7 days prior to the assessment of steady state PK.
- Overall, Keppra XR was well tolerated both in children and in adults. No subject had an SAE during this study and no subject discontinued from the study due to an AE.

- The results from the current submission (Study N01340) show comparable dose-normalized steady-state C_{max} and AUC of pediatrics 12-16 and adults 18- 55, based on dense sampling. Therefore, these results allow providing dosing recommendations in the 12-16 age group, similar to these in adults: Treatment should be initiated with a dose of 1000 mg once daily in pediatrics 12-16. The daily dosage may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg.

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 Drug/Drug Product Information:

Dosage Forms:
Keppra injection contains 100 mg of levetiracetam per mL. It is supplied in single-use 5 mL vials containing 500 mg levetiracetam, water for injection, 45 mg sodium chloride, and buffered at approximately pH 5.5 with glacial acetic acid and 8.2 mg sodium acetate trihydrate. Keppra injection must be diluted prior to intravenous infusion.
Keppra XR is available as 500 mg and 750 mg extended-release tablets for oral administration.
Inactive ingredients: colloidal anhydrous silica, hypromellose, magnesium stearate, polyethylene glycol 6000, polyvinyl alcohol-partially hydrolyzed, titanium dioxide (E171), Macrogol/PEG3350, and talc.

Strengths: 100 mg levetiracetam/ mL (Keppra IV); 500 mg and 750 mg (Keppra XR)

Indication:
Keppra injection: adjunct therapy in patients with the following seizure types when oral administration of Keppra is temporarily not feasible:
- Partial onset seizures in patients one month of age and older with epilepsy
- Myoclonic Sseizures in patients 12 years of age and older with juvenile myoclonic epilepsy
- Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy

Keppra XR: adjunctive therapy in the treatment of partial onset seizures in patients ≥12 years of age with epilepsy

Pharmacologic Class: antiepileptic drugs (AEDs)

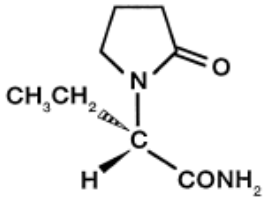
Chemical Name: (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide

Company or laboratory code(s): NA

Molecular formula: $C_8H_{14}N_2O_2$

Molecular mass: 170.21

Chemical structure:



Physical Characteristics: Levetiracetam is a white to off-white crystalline powder with a faint odor and a bitter taste. 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.

2.1.2 Mechanism of action and therapeutic indication:

The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown. *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.

2.1.3 Proposed dosages and route of administration:

Keppra IV: Same dosing as described in the most current labeling for oral Keppra in pediatric patients:

(b) (4)

[redacted]

Keppra XR in patients ≥12 years of age: Same dosing and route of administration as for adults described in the most current labeling: 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.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

The safety and effectiveness of the IV formulation is based upon adequately controlled studies of safety and effectiveness in pediatric populations using the oral formulations, as well as pharmacokinetic studies N01274 and N01275 (current submission) demonstrating comparable exposure in the oral and IV formulations. Safety information specific to intravenous use was derived from the pharmacokinetic studies.
Studies N01274 and N01275 were open-label, single-arm trials with LEV 15-min IV infusions for a maximum of 4.5 days in 33 subjects between 4 and 16 years of age and in 19 subjects between 1 month and below 4 years of age, respectively.
The effectiveness of Keppra XR as adjunctive therapy (added to other antiepileptic drugs) was established in one multicenter, randomized, double-blind, placebo-controlled clinical study that enrolled patients down to the age of 12. In addition (current submission), an open label, multicenter, parallel-group, two-arm study (N01340) was conducted to compare the pharmacokinetics of Keppra XR in pediatric patients (aged 12-16 years old) with epilepsy and in adults (aged 18-55 years old) with epilepsy. Keppra XR oral tablets (1000mg to 3000mg) were administered once daily with a minimum of 4 days and a maximum of 7 days of treatment to twelve children and 13 adults in the study.
Please refer to the Individual Studies Review for details.

2.2.2 What are the clinical endpoints and how are they measured in clinical pharmacology and clinical studies?

Not applicable (NA), pharmacokinetic (PK) studies only were conducted.

2.2.3 What are the characteristics of exposure/effectiveness relationships?

NA

2.2.4 What are the characteristics of exposure-safety relationships?

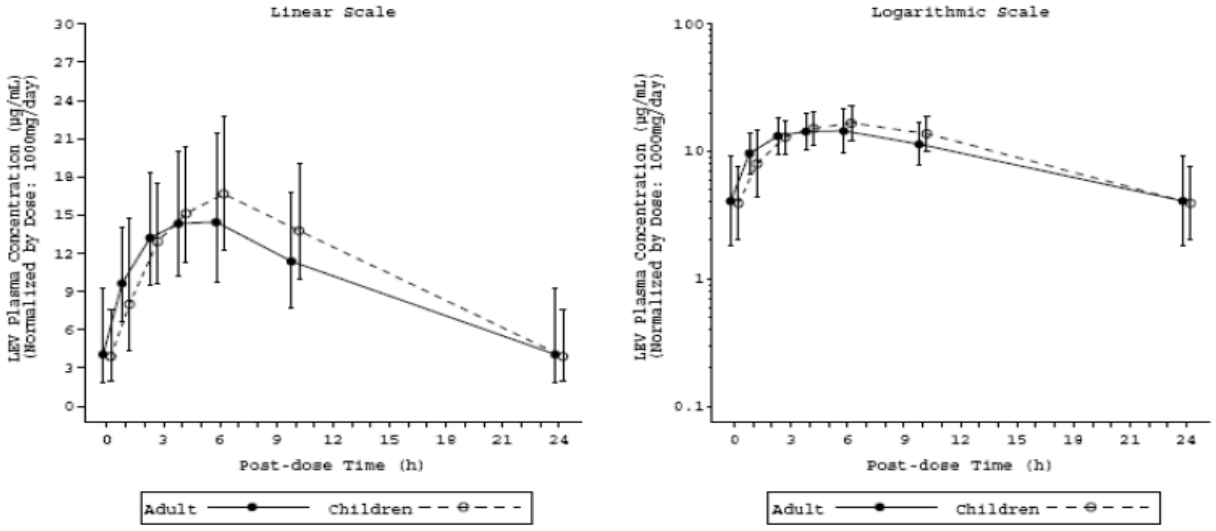
NA

2.2.5 Are the proposed dosage regimens adequately supported by the clinical trials?

Yes.

Keppra XR: The proposed dosage regimens for Keppra XR in pediatric patients aged 12 – 16 years are adequately supported by PK bridging between pediatrics and adults. Study N01340 showed comparable levetiracetam PK exposures in children aged 12 years – 16 years and adults aged 18 years – 55 years receiving equivalent doses, i.e. 1000 mg to 3000 mg per day, as shown in Figure 1 and Table 1.

Figure 1 Mean observed levetiracetam plasma concentrations versus time profies for adults and children in study N01340



Source: Figure 9:1 on page 50 in sponsor's clinical study report N01340

Table 1 Comparison of levetiracetam PK exposures between children and adults in study N01340

Parameter	Normalization	Geometric mean (SE)	
		Children (N=12)	Adults (N=10)
C_{max} (µg/mL)	normalized to LEV 1000mg	17.3 (8.6)	14.9 (11.1)
AUC_τ (µg*h/mL)		265 (8.8)	236 (12.7)
C_{max} (µg/mL)	normalized to LEV 1mg/kg	1.27 (4.8)	1.24 (7.8)
AUC_τ (µg*h/mL)		19.4 (5.7)	19.6 (10.8)
CL/F (L/h)	Not applicable	3.78 (8.9)	4.23 (12.7)
		Median (range)	
t_{max} (h)		5.90 (2.50 to 6.07)	5.93 (2.45 to 6.05)

Source: Table 9:1 on page 52 in sponsor's clinical study report N01340

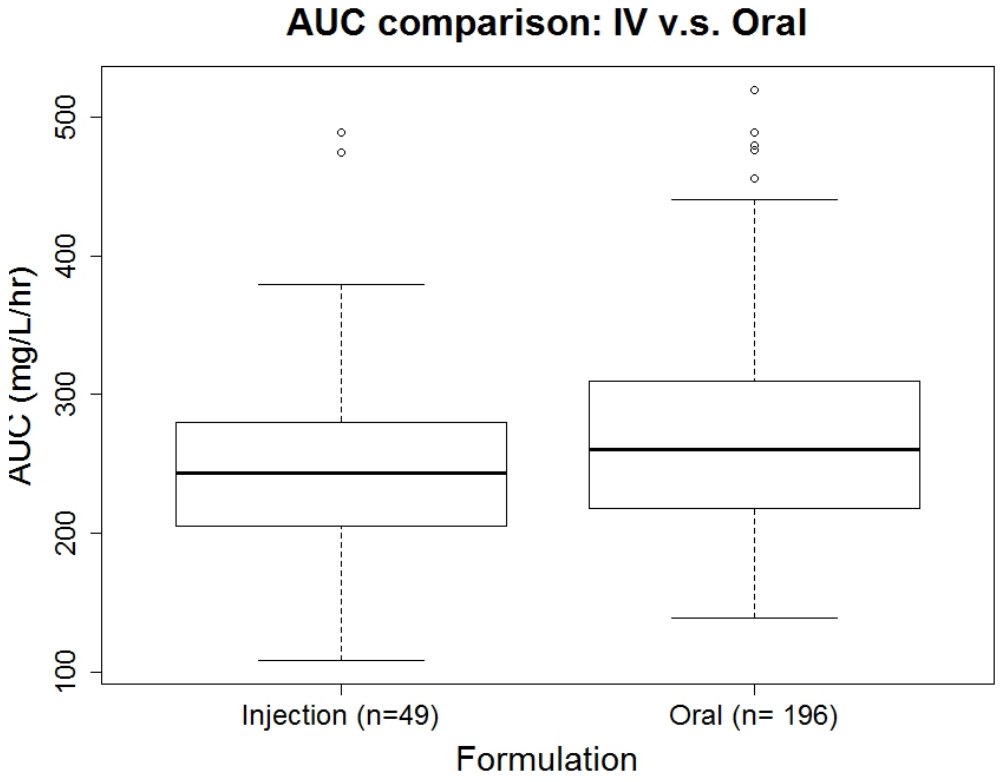
Keppra IV: The intraveneous formulation of Levetiracetam was approved in adults based on bioequivalence to the oral formulation. PK bridging between the intravaneous formulation and oral formulation in the same pediatraic age groups further supported the proposed dosage regimens for Keppra injection in pediatric patients aged 1 month – 16 years.

A population pharmacokinetic analysis was performed using plasma concentration-time data from 2 open-label phase 2 safety, tolerability, and pharmacokinetic pediatric studies (N01274 and N01275), where levetiracetram was administrated as a 15-minute IV infusion. Levetiracetam plasma concentration-time profiles from 49 subjects were used for non-linear mixed effects modeling using NONMEM. A two-compartment pharmacokinetic model adequately described the data. Body weight was incorporated

into the model on V and CL using allometric principles. A factor based on age was also incorporated into the final model to take into account the renal maturation on CL.

Steady-state PK exposures, i.e. steady-state AUCs, were derived from the population PK model and the model derived steady-state AUCs were comparable to those in pediatric patients receiving equivalent doses of Keppra oral solution, as shown in Figure 2.

Figure 2 Comparison of dose-normalized AUC between intraveneous and oral formulations



AUC normalized at 20 mg/kg

2.2.6 Does Levetiracetam prolong QT or QTc interval?

No new information on QT/QTc interval.

2.2.7 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Levetiracetam was measured by two validated LC-ESI/MS/MS assays. The initial method using (b) (4) as internal standard (IS) was re-validated using Levetiracetam-d6 as IS. The two methods were cross-validated for both matrix (plasma and saliva) using study samples initially quantified with the method using (b) (4) as IS and reanalyzed with the method using Levetiracetam-d6 as IS.

Both methods had a lower limit of quantification of 0.100 μg/mL for LEV in plasma and 1.00 μg/mL in saliva. Details are provided in the Individual Studies Review and in Section 2.6.

2.2.8 What are the general ADME characterstics of LEV?

No new clinical pharmacology information is provided in these submissions. The sponsor plans to include the same information in their labeling as is provided in the currently approved Keppra IV and Keppra XR labels.

PK information from Keppra labels:

- BCS class 1 drug (high solubility, high permeability)
- The oral bioavailability of LEV tablets is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption
- Equivalent doses of Keppra IV and Keppra oral result in equivalent C_{max}, C_{min}, and total systemic exposure to LEV when the Keppra IV is administered as a 15 minute infusion in adults
- Linear and time-invariant PK
- Low intra- and inter-subject PK variability
- LEV 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.
- LEV plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. LEV is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. LEV elimination is correlated to creatinine clearance.
- LEV and its major metabolite are less than 10% bound to plasma proteins

2.2.9 What are the basic pharmacokinetic parameters of LEVafter single and multiple doses?

NA

2.2.10 Do the pharmacokinetic parameters change with time following chronic dosing?

No new clinical pharmacology information is available, see Sect 2.2.8.

2.2.11 What is the variability in the PK data?

Keppra XR: In study N01340, PK variability was low for both AUC_τ and C_{max} in children and adults (5.7% and 10.8% for AUC_τ and 4.8% and 7.8% for C_{max} in children and adults, as expressed as %SE, respectively, when normalized to LEV 1mg/kg).

Keppra IV: The population PK model for Keppra IV infusion in pediatric patients aged 1 month – 16 years showed low inter-individual variability for both CL (22.7%) and V (20.4%), but much higher for k_{12} (143.5%), as shown in Table 2.

Table 2 Parameter Estimates for the final population PK model for Keppra IV in pediatric patients

Parameter	Estimate [95% CI]	Precision (%CV)[a]
Clearance		
θ_{CL} (L/h)	1.90 [1.57- 2.23]	8.79%
$\theta_{BW,CL}$	0.53 [0.293 – 0.767]	22.8%
$\theta_{MF,CL}$	0.181 [0.035 – 0.327]	41.2%
$\theta_{MF,exp,CL}$	1.56 [0.419 – 2.70]	37.3%
Volume		
θ_{V} (L)	11.9 [10.5-13.3]	6.21%
$\theta_{BW,V}$	0.776 [0.664 – 0.888]	7.35%
Rate constant		
$k_{12}= \theta k_{12}$		
θk_{12} (h^{-1})	8.72 [0.135 – 17.3]	50.2%
$k_{21}= \theta k_{12} * \theta_{scal,k21}$		
$\theta_{scal,k21}$	0.633 [0.357 – 0.909]	22.3%
Variability	**Estimate in %CV[b]**	**Precision (%CV)[a]**
Inter-individual variability on CL	22.7%	27.6%
Inter-individual variability on V	20.4%	28.5%
Inter-individual variability on K12	143.5%	98.1%
Residual variability in concentrations	27.2%	22.6%

Source: Table 10:7 on page 43 in sponsor's popPK study report CL0010

2.2.12 How do the pharmacokinetics of the drug in healthy volunteers compare to that in patients?

No new clinical pharmacology information is available.

2.2.13 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

No new clinical pharmacology information is available.

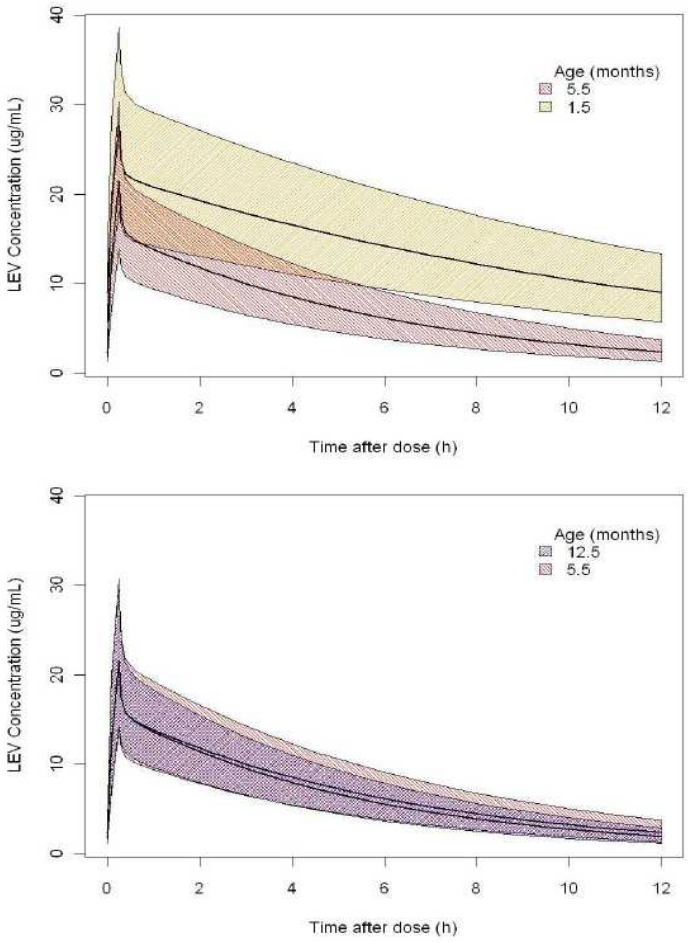
2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

Keppra XR: No new clinical pharmacology information is available for Keppra XR.

Keppra IV:
The only covariates explaining the variability were BW on both CL and V, followed by a maturation factor based on age taking into account the renal maturation on CL. The maturation factor, which is a hyperbolic function of age, was found to significantly affect leveteracetam CL. The clinical significance of such maturation factor was evaluated and confirmed by simulating steady-state concentraton profiles for children of the same body weight, but different ages. The results of the simulation are presented in Figure 3, which shows a greater than 20% effect of such maturation factor on leveteracetam CL and PK in the the youngest age range (between 1.5 and 5.5 months old), but much less effect in the older age range (between 5.5 and 12.5 months old). Such results illustrate that the maturation factor palys an important role on leveteram PK at very early age, and its effect would be negligible after certain age.

Figure 3 Simulated plasma concentration time profiles in children 1.5 months and 5.5 months old with the same BW of 6.1 kg (upper panel) and 5.5 months and 12.5 months old with the same BW of 9.0 kg (lower panel) receiving 10 mg/kg bid.



Source: Figure 10:8 on page 40 in sponsor's popPK study report CL0010

Conclusion

- The only covariates explaining the variability were BW on both CL and V, followed by a factor based on age taking into account the renal maturation on CL. However, the maturation factor had a greater than 20% effect on the exposure parameters in the youngest age range only (between 1.5 and 5.5 months old).

2.4 EXTRINSIC FACTORS

Drug-drug interaction from Keppra labels:

- In vitro data on metabolic interactions indicate that LEV is unlikely to produce, or be subject to, pharmacokinetic interactions.
- Potential PK interactions of or with immediate-release LEV were assessed in clinical pharmacokinetic studies (phenytoin, valproate, warfarin, digoxin, oral contraceptive, probenecid). In addition, the potential drug interactions between KEPPRA and other

AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone and valproate) were assessed by evaluating the serum concentrations of LEV and these AEDs during placebo-controlled clinical studies. These data indicate that LEV does not influence the plasma concentration of other AEDs and that these AEDs do not influence the pharmacokinetics of LEV.

- Effect of AEDs in Pediatric Patients: There was about a 22% increase of apparent total body clearance of levetiracetam when it was co-administered with enzyme -inducing AEDs. Dose adjustment is not recommended. Levetiracetam had no effect on plasma concentrations of carbamazepine, valproate, topiramate, or lamotrigine.

The statement about the Effect of AEDs in Pediatric Patients is based on the Clinical Pharmacology review, NDA 21035, 03/18/2008.
However, the reviewer also stated the following in the review:
Based on population PK analysis, the sponsor demonstrated that clearance in pediatric patient in various age groups is increased by about 20% when levetiracetam is co-administered with another enzyme inducer or neutral drug. It is to note that the sponsor did not specify the name of drugs which are defined as inducer or neutral drugs. The results appear difficult to interpret because the same subject can receive multiple co-medications. More importantly, 20% change in exposure usually does not lead to dose adjustment.
Furthermore, extensive drug-drug interaction is not expected for levetiracetam. In adults, 66% of the administered drug is eliminated in urine as parent compound. The major mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. Levetiracetam is not extensively metabolized in human. The major metabolic pathway is enzymatic hydrolysis of acetamide group, and it is not dependant on P450 isoenzyme.

The popPK in the current studies did not show an effect of AED on LEV clearance.
However, the current population PK analysis may not be powered to detect the effect of concomitant AED on LEV clearance probably due to small percentage of subjects (12 subjects; less than 25%) receiving an inducing AED. And 4 out of the 12 subjects were younger than 6 month old and 1 out of 12 was 6.6 months old. Therefore, the effect of inducing AED on LEV clearance might be partly compensated by the decreased clearance due to ongoing renal maturation at very young age. However, even if a 20% increase in exposure in response to enzyme-inducing AED co-administration was detected, dose adjustment would still not be recommended considering the reported broad efficacy and safety margin of LEV and the therapeutic approach of individual up-titration.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on the BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Levetiracetam is a BCS class 1 drug (high solubility, high permeability) (Keppra labels).
No new clinical pharmacology information is available

2.5.2 Is the proposed to-be-marketed formulation of Levetiracetam ER bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

NA

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of Levetiracetam ER in relation to meals or meal types?

No new clinical pharmacology information is available**.**

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

Yes.
Levetiracetam was measured by two validated LC-ESI/MS/MS assays. The initial method using (b) (4) as internal standard (IS), V3.3.0, was re-validated using Levetiracetam-d6 as IS (version 4.0.0). The only difference between these methods is the IS used: a chemical analogue (b) (4) in method V3.3.0 and an isotopically labeled standard in method V4.0.0. After addition of IS, ucb L059 and the IS were extracted from plasma by Solid Phase Extraction (SPE) and then analyzed by reversed phase ultra- high pressure liquid chromatography (UPLC) in gradient mode with electrospray tandem mass spectrometry (MS/MS) detection using positive multiple reaction monitoring (MRM) mode.
Both methods had a lower limit of quantification of 0.100 µg/mL for LEV in plasma and 1.00 µg/mL in saliva.
The two methods were cross-validated for both matrix (plasma and saliva) using study samples initially quantified with the method using (b) (4) as IS and reanalyzed with the method using Levetiracetam-d6 as IS. A cross validation between methods V3.3.0 and 4.0.0 was performed on QC samples and on study samples from Clinical Study Number N01274 (NCD2088). The QC results were within the acceptance criteria. Also, more than 67% of the selected samples for cross validation were within the acceptance criteria. Therefore, bioanalytical method using (b) (4) as IS and bioanalytical method using levetiracetam-D6 as IS could be considered equivalent in the quantification of levetiracetam in human plasma and saliva samples.

Details of the cross-validation between methods V3.3.0 and V4.0.0 are presented in the Individual Studies Review.

The validation results (version 4.0.0) are presented in the table below.

Validation Parameters for Levetiracetam Bioanalytical Assay V 4.0.0

Regression type	Linear
Weighing factor	$1/x^2$
Coefficient of determination (n=3)	$r^2>0.99$
Limits of quantification (LLOQ and ULOQ) (µg/mL)	0.100–100 (plasma)
Limit of detection (µg/mL)	ca 0.013
Intra-run precision on calibration measurements RSD (%)	≤ 4.2
Intra-run accuracy on calibration measurements Relative error (%)	≤ |4.7|
Inter-run precision on calibration measurements RSD (%)	≤ 3.7
Inter-run accuracy on calibration measurements Relative error (%)	≤ |2.5|
Inter-run precision on QC samples RSD (%)	≤ 5.5
Inter-run accuracy on QC samples Relative error (%)	≤ |2.5|
Validated matrices	Human Li-heparinated plasma Human EDTA plasma Human serum Human saliva (dil. 10-fold with human Li-hep plasma)
Stability of reconstructed extracts at 10°C	96 hours*
Stability in matrix at RT	168 hours in human Li-heparinated plasma* 168 hours in human EDTA plasma* 24 hours in human serum* 168 hours in human saliva*
Stability in matrix at -20°C	1001 days in human Li-heparinated plasma 419 days in human EDTA plasma* 58 days in human serum* 1001 days in human saliva
Stability in matrix on dry ice (–78°C)	192 hours in human Li-heparinated plasma
Matrices and No. of freeze/thaw cycles for which stability exists	3 cycles in human EDTA plasma* 3 cycles in human serum* 3 cycles in human saliva
Stability of stock solutions in H_2O	14 months at -20°C followed by 4h at RT
Stability of IS working solution at 5.00µg/mL in H_20, 0.1% TFA-pH=2.50	66d at -20°C followed by 24h at RT*

*Stability data obtained during this validation.

3.0 DETAILED LABELING RECOMMENDATION

The reviewer's labeling recommendations are shown by track changes to the sponsor proposed labels for Keppra IV and XR. These labeling changes should be incorporated in the revised labels.

8.4 Pediatric Use

(b) (4)

12.3 Pharmacokinetics

Pediatric Patients

(b) (4)

Oral Formulations

(b) (4)

Keppra XR

8.4 Pediatric Use

Safety and effectiveness in pediatric patients 12 years of age and older has been established based on PK data in adults and adolescents using KEPPRA XR and pediatric studies using KEPPRA. *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)].*

Safety and effectiveness of KEPPRA XR in patients below the age of (b) (4) 12 years have not been established.

12.3 Pharmacokinetics

Pediatric Patients

(b) (4)

An open label, multicenter, parallel-group, two-arm study was conducted to evaluate the pharmacokinetics of Keppra extended release (XR tablet) in pediatric patients (13 to 16 years old) and in adults (18 to 55 years old) with epilepsy. Keppra XR oral tablets (1000mg to 3000mg) were administered once daily with a minimum of 4 days and a maximum of 7 days of treatment to 12 pediatric patients and 13 adults in the study. Dose -normalized steady-state exposure parameters, C_{max} and AUC were comparable to those in adults.

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