CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204417Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Memo

PRODUCT (Generic Name):	Levetiracetam Extended Release (1000 and 1500 mg)
PRODUCT (Brand Name):	ELEPSIA XR
NDA:	204417
DOSAGE FORM:	Extended-Release Tablets
DOSAGE STRENGTH:	1000 mg and 1500 mg
INDICATION:	Adjunctive therapy in the treatment of partial onset seizures
NDA TYPE:	Resubmission
SUBMISSION DATE:	July 2, 2018
SPONSOR:	Sun Pharma Advanced Research Company, Ltd.
REVIEWER:	Hristina Dimova, Ph.D.
TEAM LEADER:	Angela Men, M.D, Ph.D.
OCPB DIVISION:	DCP-I
OND DIVISION:	HFD-120

This is a Resubmission after a Complete Response (CR) of a 505(b)(2) NDA. The approval is to be based on bioequivalence (BE) of ELEPSIA XR to the reference product (RLD) Keppra XR. Keppra XR, approved in 2008, is indicated for adjunctive therapy in the treatment of partial onset seizures in patients 12 years of age and older with epilepsy. Two strengths of Keppra XR are available, 500 mg and 750 mg.

Regulatory History:

- NDA 210864 submitted on 24 May 2012
- March 29, 2013: CR letter
- NDA resubmission: September 2, 2014
- March 2, 2015, approval letter
- September 23, 2015, approval was rescinded due to deficiencies of the manufacturing facilities
- March 22, 2017, CR letter

A CR letter was issued on March 29, 2013, due mainly to 30% of patients having plasma concentration-time curves that differed significantly from these observed after Keppra XR in the fed state, despite that in the fed bioequivalence (BE) study ELEPSIA XR met the BE criteria for Cmax and AUC. In Sept 2014 the sponsor addressed this issue by submitting the results of a multiple dose, relative bioavailability, switch over study to compare levetiracetam PK profiles after administration of the RLD and the proposed formulation in healthy subjects for 4 successive days (to levetiracetam steady state) when switched from fasted to fed or fed to fasted state. The NDA was approved in March 2015, then rescinded in September 2015 due to manufacturing issues.

In Sept 2016 the sponsor submitted a CR to the September 23, 2015 action letter. This CR included information to address Agency comments regarding facility deficiencies and revised draft labeling with proposed changes to dosing information for patients with renal impairment. A second CR was issued in March 2017 due to unresolved manufacturing facilities issues. In addition, the following clinical pharmacology issue was included in the CR:

PRESCRIBING INFORMATION

We are unable to include in ELEPSIA XR labeling dosing information (b) (4)

(b) (4)

No new clinical studies have been submitted in the current Resubmission after CR. The approval will be based on the results of the switch over BE study, refer to the March 2015 NDA approval above. The current NDA resubmission includes updated labeling to address the manufacturing facilities issues and additional labeling modifications to align with Keppra XR labeling approved in 2017.

The sponsor had additional changes for renal impairment; however, only labeling modifications to align with Keppra XR labeling approved in 2017 will be accepted. The March 2, 2015 approval letter included a label which both FDA and sponsor agreed on.

RECOMMENDATION

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 204417 (resubmission). The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided the sponsor agrees with the Agency's labeling recommendations.

The Clinical Pharmacology edits to the proposed label are provided below.

(b) (4)

6 Pages have been Withheld In Full as Draft Labeling Immediately Following this Page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HRISTINA DIMOVA
11/30/2018

YUXIN MEN
12/02/2018

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Levetiracetam Extended Release (1000 and 1500 mg)
PRODUCT (Brand Name):	NA
NDA:	204417
DOSAGE FORM:	Extended-Release Tablets
DOSAGE STRENGTH:	1000 mg and 1500 mg
INDICATION:	Adjunctive therapy in the treatment of partial onset seizures
NDA TYPE:	Standard
SUBMISSION DATE:	September 2, 2014
SPONSOR:	Sun Pharma Advanced Research Company, Ltd.
REVIEWER:	Hristina Dimova, Ph.D.
TEAM LEADER:	Angela Men, M.D, Ph.D.
OCPB DIVISION:	DCP-I
OND DIVISION:	HFD-120

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1.0 EXECUTIVE SUMMARY

Levetiracetam (LEV), an antiepileptic drug, was first approved in 1999 as Keppra®, an immediate release tablet. An extended release tablet, Keppra XR®, was later approved in 2008, indicated for adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. Two strengths of Keppra XR® are available, 500 mg and 750 mg. Treatment with Keppra XR 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.

An NDA for a new formulation of LEV with higher strengths (1000 mg and 1500 mg) extended-release (ER) tablets was submitted on 28 May 2012 under Section 505(b)(2), referencing Keppra XR, for the treatment of partial onset seizures in patients ≥ (b)(4) years of age with epilepsy. Three single-dose, randomized, open-label, crossover bioequivalence (BE) studies were conducted to compare the proposed formulation of Levetiracetam ER Tablets, 1500 mg to the RLD, Keppra XR Tablets (2 x 750 mg) in healthy adult subjects under fasted and fed conditions.

On March 29, 2013 a Complete Response was issued due to the following reasons:

CLINICAL PHARMACOLOGY

We acknowledge that the data from your bioequivalence (BE) studies establish that your product is bioequivalent to Keppra XR in the fasted state. However, examination of the data from your two BE studies in the fed state (Studies 131 and 272) reveals that a substantial percent of patients have plasma concentration-time curves that differ significantly between your product and Keppra XR, despite the observation that in Study 272, your product meets bioequivalence criteria for Cmax and AUC. As you know, the Division considers similarity of the overall shapes of these curves to be an important factor in deciding that two products will have similar safety and effectiveness.

In addition, the 1500 mg tablet showed dose dumping potential at the highest alcohol concentration ((b)(4) %) in the in vitro studies. The labeling of the RLD does not have a statement limiting alcohol use. This issue may potentially be resolved if you conduct an in vivo study to evaluate the impact of the observed effect in vitro.

In this NDA resubmission, the sponsor presents the results of a multiple dose, relative bioavailability, switch over study that was discussed with the Division at the End-of -Review Meeting. This study was designed to compare the LEV PK profiles after administration of the RLD and the proposed formulation in healthy subjects for 4 successive days (to LEV steady state) when switched from fasted to fed or fed to fasted state. The results of this study demonstrated that the ratios of the least-square means (and 90% confidence intervals) of the Test to Reference product for LEV after day 2 and day 4 of dosing (i.e day on which subjects were switched from fasting to fed condition) were within the BE limits for AUC_{0-24} and C_{max} under fed condition, In addition, even though about 20% of the subjects in the study had a "prolonged pattern of release" following administration of the Test ER Tablets with food, this did not result neither in potentially sub-therapeutic concentrations nor higher peak concentrations than that of the reference product when subjects were dosed on the following day.

Based on additional data submitted by the sponsor (25 February 2013), ONDQA concluded that an in vivo alcohol interaction study is not needed.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 204417 (resubmission). The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided the sponsor agrees with the Agency's labeling recommendations.

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The clinical pharmacology and biopharmaceutics findings are as follows:

- Levetiracetam ER Tablets, 1500 mg were bioequivalent to Keppra XR® tablets, 2 x 750 mg in the fasted state.
- The results of a multiple dose, relative bioavailability, switchover study demonstrated that the ratios of the least-square means (and 90% confidence intervals) of the Test (Levetiracetam ER Tablets, 1500 mg) to Reference (Keppra XR® tablets, 2 x 750 mg) product for LEV after Day 2 and Day 4 of dosing were within the BE limits for AUC_{0-24} and C_{max}.
- About 20% of the subjects in the study had a "prolonged pattern of release" following administration of the Test ER Tablets with food, however this did not result neither in potentially sub-therapeutic concentrations nor higher peak concentrations than that of the reference product when subjects were dosed on the following day.
- There was no significant difference in clearance adjusted for body weight between male and female subjects in the study

In summary, although some subjects had prolonged absorption when the new drug product was dosed with food, there should be no clinically meaningful impact (i.e., trough and peak concentrations were similar to those of subjects without altered profiles as well as subjects dosed with the reference product).
No new clinical pharmacology information is available for Levetiracetam ER Tablets, nor was any new information identified in a search of the published literature. The sponsor plans to include the same information in their labeling as is provided in the currently approved Keppra XR® label with the exception of the modifications to Absorption and Distribution Section by adding their BE results.

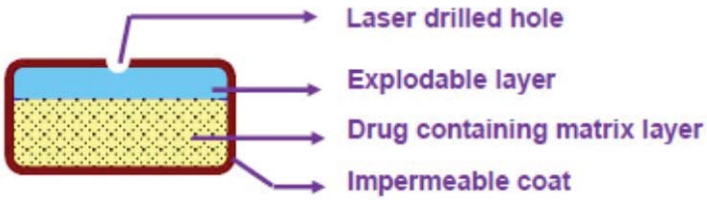
2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 Drug/Drug Product Information:

Dosage Form: The proposed product is a "Wrap Matrix" dosage form consisting of: Bilayer tablet (Drug layer and Openable layer), Functional coat and Top coat. Laser drilling is done on color layer side only.

Wrap Matrix: Dosage form Design



Strengths: 1000 mg and 1500 mg

Indication: adjunctive therapy in the treatment of partial onset seizures in patients ≥ (b) (4) years of age with epilepsy

Pharmacologic Class: antiepileptic drugs (AEDs)

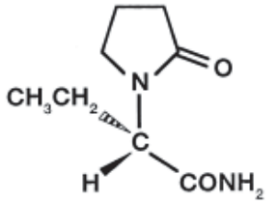
Chemical Name: (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide

Company or laboratory code(s): SPARCL

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.

Formulation:

Components	Amount (mg)/Tablet		Amount % w/w
Strength	1000 mg	1500 mg	1000 mg and 1500 mg
	(b) (4)		
Levetiracetam, USP	1000.00	1500.00	(b) (4)
Povidone (b) (4), USP		(b) (4)	
Hypromellose (b) (4) (b) (4)			
Amino Methacrylate Copolymer, NF (b) (4) (b) (4)			
Colloidal silicon dioxide, NF			
Magnesium stearate, NF (b) (4)			
Talc, USP (b) (4)			

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.

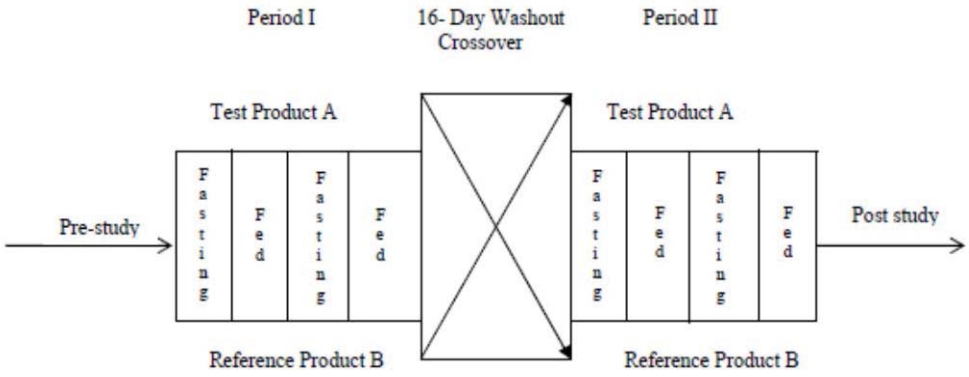
2.1.3 Proposed dosages and route of administration:

Same dosing and route of administration as described in the most current labeling for Keppra XR®: 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?

In the original NDA submission, three single-dose, randomized, open-label, crossover bioequivalence (BE) studies were conducted to compare the final proposed formulation of Levetiracetam ER Tablets, 1500 mg to the RLD, Keppra XR® Tablets (2 x 750 mg) in healthy adult subjects under fasted and fed conditions. A waiver of the need for an in vivo study of the lower strength is included, supported by the composition proportionality of the tablets and the results of multi-media *in vitro* dissolution testing. *In vitro* dissolution in alcoholic media has also been studied.
In the current NDA resubmission, a multiple dose, relative bioavailability, switchover study was conducted to compare the LEV PK profiles after administration of the RLD and the proposed formulation in healthy subjects for 4 successive days (to LEV steady state) when switched from fasted to fed or fed to fasted state.



This study was conducted to reply the CR dated March 29, 2013. There is no efficacy trial conducted to support its approval.

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

Not applicable (NA), bioequivalence studies only 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. Levetiracetam ER Tablets, 1500 mg were bioequivalent to Keppra XR® tablets, 2 x 750 mg in the fasted and fed states.
A waiver of the need for in vivo study of the lower strength is supported by the composition proportionality of the tablets and multi-media in vitro dissolution testing (request submitted in the original NDA). As appropriate for an extended-release dosage form, in vitro dissolution in alcoholic media has also been studied.

The statistics of the LEV pharmacokinetic parameters after Day 2 and Day 4 dosing (i.e day on which subjects were switched from fasting to fed condition) are presented below.

AUC_{0-24} After Day 2 Dosing

$LnAUC_{0-24}$	**Levetiracetam 1500 mg Extended Release tablets Test (A)**	**Keppra XR™ (Levetiracetam) 750 mg (2 x 750mg dose) Extended Release Tablets Reference (B)**
Least Squares Means	6.07	6.13
Least squares Geometric Means	434.18	458.17
Ratio of Least-Squares Geometric Means (A/B)%	94.76	
90% Geometric C.I.	91.02 to 98.67	
Intra-Subject CV %	9.83	

C_{max} After Day 2 Dosing

LnC_{max}	**Levetiracetam 1500 mg Extended Release tablets Test (A)**	**Keppra XR™ (Levetiracetam) 750 mg (2 x 750mg dose) Extended Release Tablets Reference (B)**
Least Squares Means	3.33	3.44
Least squares Geometric Means	27.95	31.09
Ratio of Least-Squares Geometric Means (A/B)%	89.88	
90% Geometric C.I.	84.96 to 95.09	
Intra-Subject CV %	13.75	

AUC_{0-24} After Day 4 Dosing

$LnAUC_{0-24}$	**Levetiracetam 1500 mg Extended Release tablets Test (A)**	**Keppra XR™ (Levetiracetam) 750 mg (2 x 750mg dose) Extended Release Tablets Reference (B)**
Least Squares Means	6.13	6.13
Least squares Geometric Means	459.63	461.73
Ratio of Least-Squares Geometric Means (A/B)%	99.55	
90% Geometric C.I.	96.30 to 102.90	
Intra-Subject CV %	8.06	

C_{max} After Day 4 Dosing

LnC_{max}	Levetiracetam 1500 mg Extended Release tablets Test (A)	Keppra XR™ (Levetiracetam) 750 mg (2 x 750mg dose) Extended Release Tablets Reference (B)
Least Squares Means	3.39	3.44
Least squares Geometric Means	29.59	31.14
Ratio of Least-Squares Geometric Means (A/B)%	95.04	
90% Geometric C.I.	91.75 to 98.44	
Intra-Subject CV %	8.57	

In addition, the variability (CV%) in LEV AUC and C_{max} after administration of the Test formulation was similar to that of the Reference.

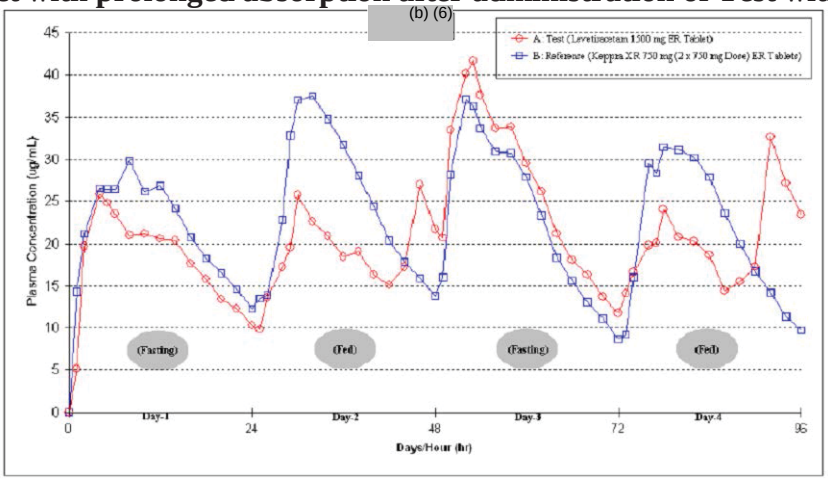
Summary of Levetiracetam Pharmacokinetic Results

Pharmacokinetic Parameters (N =34)								
Day after dosing	Levetiracetam 1500mg ER Tablet Test (A)				Keppra XR™ (Levetiracetam) 750 mg (2x750 mg dose) ER tablet Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-24} (µg.h/mL)								
2	448.7392	±	115.77194	25.8	471.3419	±	112.53446	23.9
4	473.5550	±	116.20887	24.5	475.9736	±	121.32978	25.5
C_{max} (µg/mL)								
2	28.8533	±	6.76426	23.4	32.0157	±	8.46419	26.4
4	30.5734	±	7.60610	24.9	32.0387	±	7.80383	24.4
T_{max} (hr)								
2	8.265	±	4.7820	57.9	6.265	±	2.0495	32.7
4	7.706	±	3.9583	51.4	6.118	±	1.2972	21.2
*T_{max} (hr)								
2	6.00 (4.00 - 22.00)	-	-	-	6.00 (4.00 - 14.00)	-	-	-
4	6.00 (4.00 - 20.00)	-	-	-	6.00 (5.00 - 12.00)	-	-	-
C_{min} (µg/mL)								
1	8.0134	±	2.95074	36.8	7.9089	±	2.81859	35.6
2	11.6124	±	5.38287	46.4	9.4230	±	3.25196	34.5
3	9.8020	±	3.70441	37.8	9.1178	±	3.56334	39.1
4	11.5450	±	4.95630	42.9	9.4323	±	3.21620	34.1

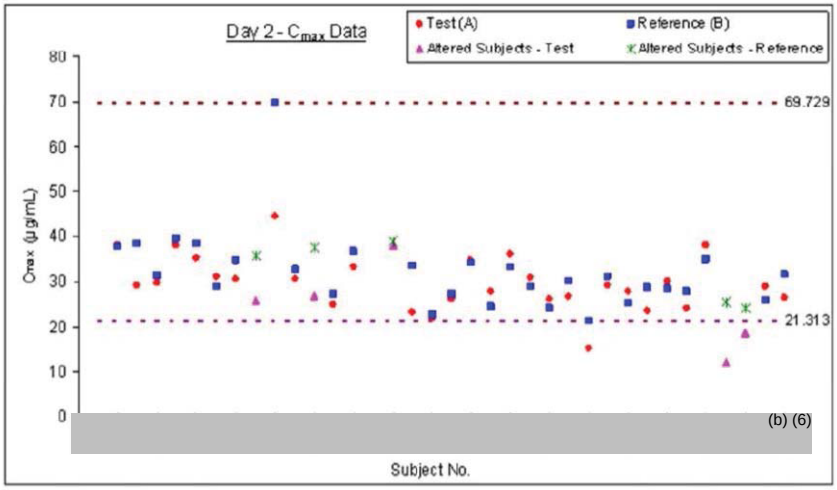
*Median values (range) are presented. Source: Appendix 16.2.6.1

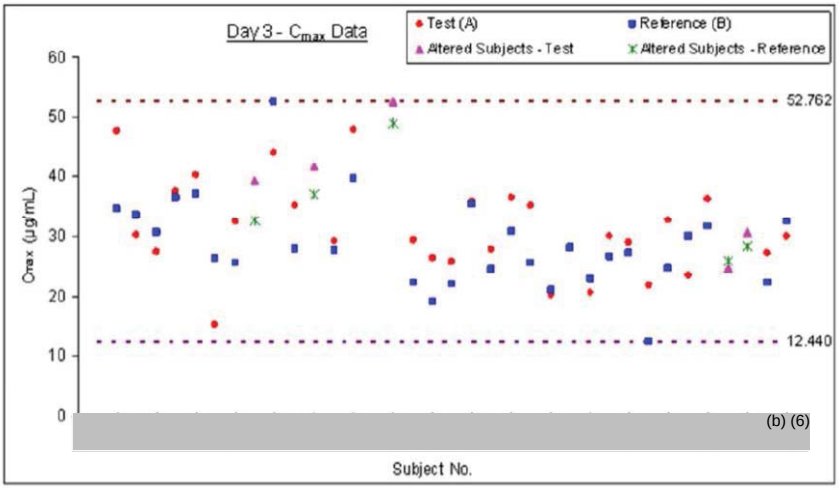
Although some subjects (about 20%) had prolonged absorption when the proposed test product was dosed with food (see one example below), this did not result in increased individual LEV C_{max} on the following day over that of the individual C_{max} of the reference product at that particular day, see scatterplots below.

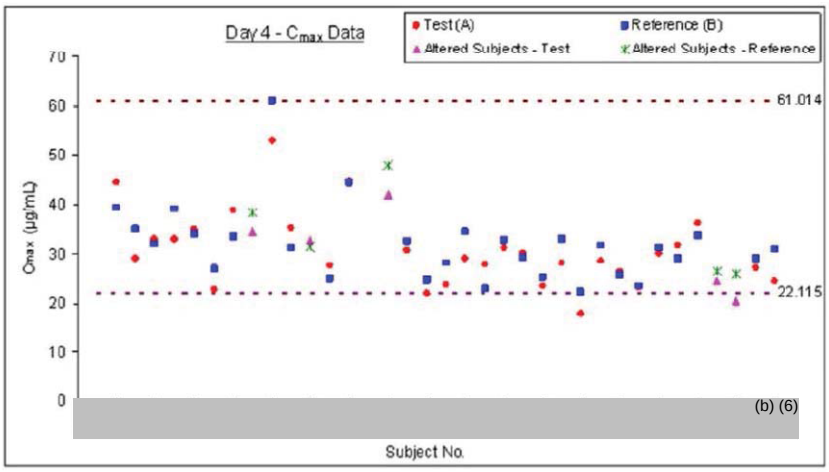
Subject with prolonged absorption after administration of Test with food



Scatterplots of Individual Cmax



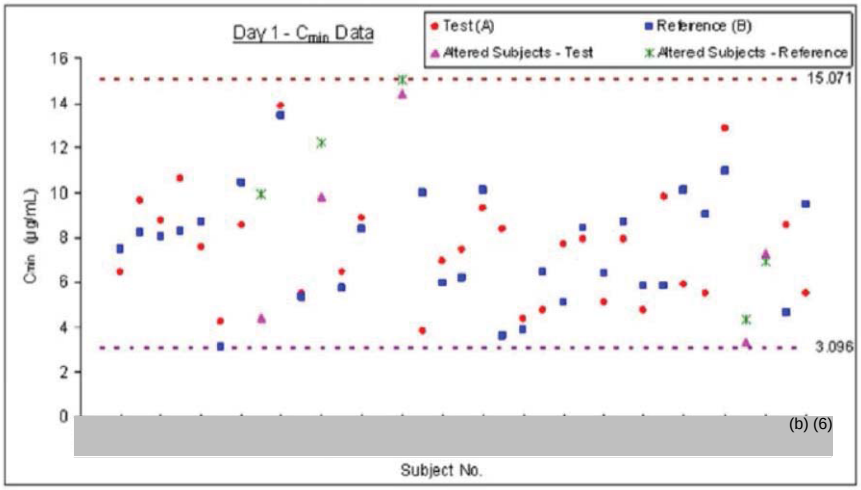


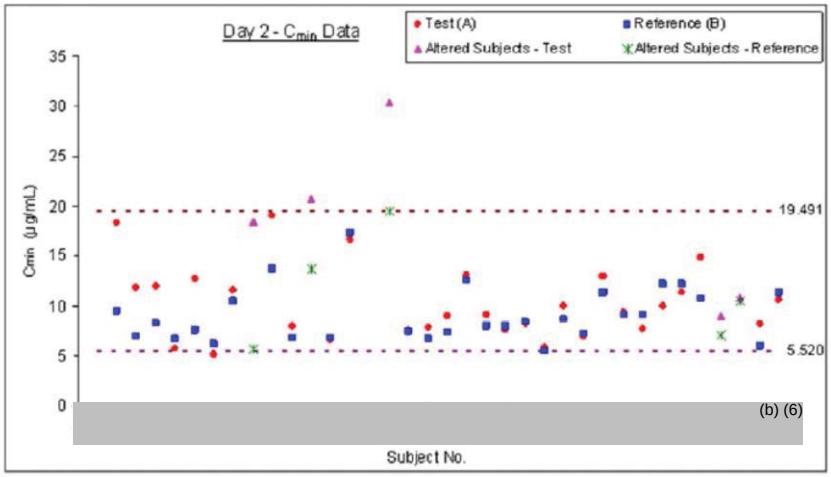


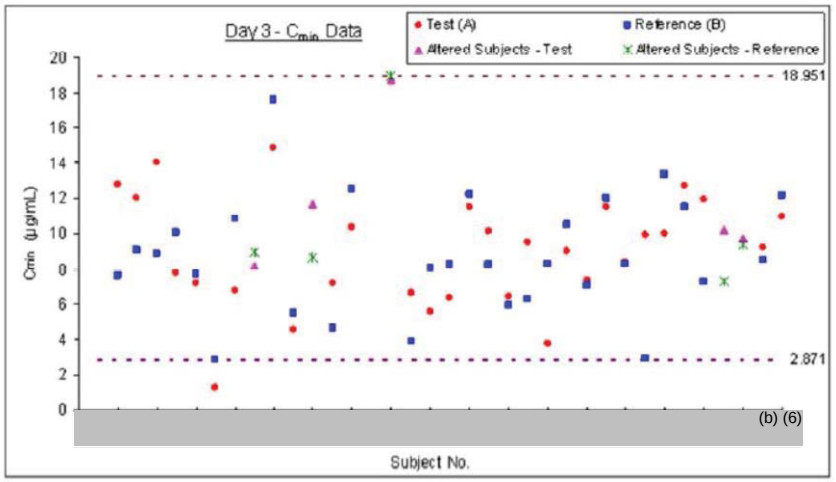
Note: The dashed lines represent the minimum and maximum value of the reference product at a particular day.

In addition, the C_{min} of the Test formulation were not below that of the Ref on any of the dosing days, see scatterplots below. Therefore, there should be no decrease in efficacy when a subject is switched from Ref to Test formulation.

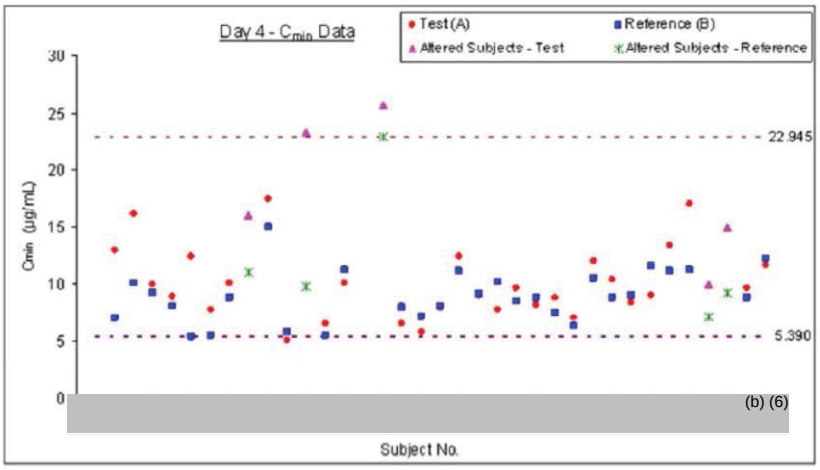
Scatterplots of Individual Cmin







Note: The only Cmin below the dashed line on Day 3 (minimum and maximum value of reference product at particular day) belongs to Subject number (b) (6) who had compliance issues.



2.2.6 Does Levetiracetam prolong QT or QTc interval?

NA

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

Yes. A Pre-Approval Data Validation Inspection, conducted by the Office of Scientific Investigations (January 15, 2013), found the method validation and the assay of the plasma samples in the original NDA submission to be acceptable. On Oct 21, 2014 the Division of Bioequivalence and GLP Compliance Office of Scientific Investigations recommended accepting data for NDA 204417 Resubmission without on-site inspection of the clinical and bioanalytical sites (of the new Study PKD_14_049) based on the satisfactory inspections in recent years and the similarity of the methodologies and processes in the previous submission [studies PKD_10_130 (Fasted) & PKD_10_272 (Fed)], which were inspected by the Division in 2013.

Overview of Original Bioanalytical Method (ATP_02_LVT) and Current Method Used for "Switching" Study (ATP_03_LVT and ATP_04_LVT)

	Original Studies	"Switch Over" Study No. PKD_14_049	
ATP No.	ATP_02_LVT	ATP_03_LVT	ATP_04_LVT
Method Validation No.	MV_LVT_016A	MV_LVT_016B	MV_LVT_016B
Anti-coagulant	K_2 EDTA		
Extraction Type	SPE		
Mobile Phase	Methanol:Acetonitrile (80:20) : 2 mm Ammonium acetate; pH:3.4 (90:10)		
Column	Symmetry C18, 75×4.6 mm, 3.5 µ		
Injection Volume	2 µL		
Range	0.220 - 39.984 µg/mL	0.199 - 39.887 µg/mL	
Diluent	45:55(methanol:water)	40:60 (methanol:water)	
Flow Rate	0.650 mL/min	1.0 mL/min (splitter)	
Auto Sampler Temperature	10°C	6°C	
Instrument	API-2000 and Shimadzu HPLC	API-4000 and Dionex UHPLC	
Run Time (minutes)	2.5	2.0	

2.2.8 What are the general ADME characterstics of Levetiracetam ER?

No new clinical pharmacology information is available for Levetiracetam ER Tablets. The sponsor plans to include the same information in their labeling as is provided in the currently approved Keppra XR® labeling (Aug 2014) with the exception of the modifications to Absorption and Distribution Section by adding their BE results.

Modifications to Absorption and Distribution Section proposed by the sponsor:

Section	Keppra XR® (most currently approved [August 2014])	Levetiracetam Extended Release Tablets
12.3	**Pharmacokinetics** Overview Bioavailability of KEPPRA XR tablets is similar to that of the immediate-release Keppra Tablets. …	**Pharmacokinetics** Overview Bioavailability of (b) (4) (b) (4)
12.3	**Pharmacokinetics** Absorption and Distribution Extended-release levetiracetam peak plasma concentrations occur in about 4 hours. The time to peak plasma concentrations is about 3 hours longer with extended-release levetiracetam than with immediate-release tablets. Single administration of two 500 mg extended-release levetiracetam tablets once daily produced comparable maximal plasma concentrations and area under the plasma concentration versus time as did the administration of one 500 mg immediate-release tablet twice daily in fasting conditions. After multiple dose extended-release levetiracetam tablets intake, extent of exposure (AUC_{0-24}) was similar to extent of exposure after multiple dose immediate-release tablets intake. C_{max} and C_{min} were lower by 17% and 26% after multiple dose extended-release levetiracetam tablets intake in comparison to multiple dose immediate-release tablets intake. Intake of a high fat, high calorie breakfast before the administration of extended-release levetiracetam tablets resulted in a higher peak concentration, and longer median time to peak. The median time to peak (T_{max}) was 2 hours longer in the fed state. Two 750 mg extended-release levetiracetam tablets were bioequivalent to a single administration of three 500 mg extended-release levetiracetam tablets.	**Pharmacokinetics** Absorption and Distribution Extended-release levetiracetam peak plasma concentrations occur in about 4 hours. The time to peak plasma concentrations is about 3 hours longer with extended-release levetiracetam than with immediate-release tablets. (b) (4) (b) (4) After multiple dose extended-release levetiracetam tablets intake, extent of exposure (AUC_{0-24}) was similar to extent of exposure after multiple dose immediate-release tablets intake. C_{max} and C_{min} were lower by 17% and 26% after multiple dose extended-release levetiracetam tablets intake in comparison to multiple dose immediate-release tablets intake. Intake of a high fat, high calorie breakfast before the administration of extended-release levetiracetam tablets resulted in a (b) (4) (b) (4) longer median time to peak. The median time to peak (T_{max}) was **3 to 4.5 hours** longer in the fed state. **There was no effect on peak plasma concentration, however, the extent of exposure (AUC) was 21 to 25% higher.** (b) (4) **Levetiracetam ER tablets 1500 mg were bioequivalent to KEPPRA XR (2 × 750 mg) tablets in both fasted and fed states.**

2.2.9 What are the basic PK parameters of Levetiracetam ER after single and multiple doses?

The PK parameters of the Test formulation after multiple dosing in the fed and fasting states were similar to that of the Reference.

Summary of Levetiracetam Pharmacokinetic Results

Pharmacokinetic Parameters (N =34)								
Day after dosing	Levetiracetam 1500mg ER Tablet Test (A)				Keppra XR™ (Levetiracetam) 750 mg (2x750 mg dose) ER tablet Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-24} (µg.h/mL)								
2	448.7392	±	115.77194	25.8	471.3419	±	112.53446	23.9
4	473.5550	±	116.20887	24.5	475.9736	±	121.32978	25.5
C_{max} (µg/mL)								
2	28.8533	±	6.76426	23.4	32.0157	±	8.46419	26.4
4	30.5734	±	7.60610	24.9	32.0387	±	7.80383	24.4
T_{max} (hr)								
2	8.265	±	4.7820	57.9	6.265	±	2.0495	32.7
4	7.706	±	3.9583	51.4	6.118	±	1.2972	21.2
*T_{max} (hr)								
2	6.00 (4.00 - 22.00)	-	-	-	6.00 (4.00 - 14.00)	-	-	-
4	6.00 (4.00 - 20.00)	-	-	-	6.00 (5.00 - 12.00)	-	-	-
C_{min} (µg/mL)								
1	8.0134	±	2.95074	36.8	7.9089	±	2.81859	35.6
2	11.6124	±	5.38287	46.4	9.4230	±	3.25196	34.5
3	9.8020	±	3.70441	37.8	9.1178	±	3.56334	39.1
4	11.5450	±	4.95630	42.9	9.4323	±	3.21620	34.1

*Median values (range) are presented. Source: Appendix 16.2.6.1

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

No new clinical pharmacology information is available for Levetiracetam ER Tablets, see 2.2.8.

2.2.11 What is the variability in the PK data?

The variability (CV%) in AUC and Cmax of the Test formulation was similar to that of the Reference, see table under Sect 2.2.9.

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 for Levetiracetam ER Tablets, see 2.2.8.

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 for Levetiracetam ER Tablets, see 2.2.8.

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?

No new clinical pharmacology information is available for Levetiracetam ER Tablets, nor was any new information identified in a search of the published literature. All of the RLD information with respect to special populations is also applicable to Levetiracetam 1000 mg and 1500 mg ER Tablets, with the exception of use in patients with renal impairment. Levetiracetam clearance is correlated with creatinine clearance and therefore lower doses (500 to 1500 mg) are recommended in patients with moderate or severe impaired renal impairment. Since these doses cannot be achieved with the available ER tablet strengths, the sponsor proposes to modify Section 2.1 the label to "not recommended in patients with moderate or severe impaired renal impairment", this is acceptable.

Note: In addition, the sponsor proposed the following changes for gender in Sect. 12.3.

Section	Keppra XR® (most currently approved [August 2014])	Levetiracetam Extended Release Tablets
2.2	**Adult Patients with Impaired Renal Function** KEPPRA XR dosing must be individualized according to the patient's renal function status.	(b) (4)
12.3	**Pharmacokinetics** Gender Extended-release levetiracetam C_{max} was 21-30% higher and AUC was 8-18% higher in women (N=12) compared to men (N=12). However, clearances adjusted for body weight were comparable.	**Pharmacokinetics** Gender **When given in a single dose, e**~~E~~xtended-release levetiracetam C_{max} was 21-30% higher and AUC was 8-18% higher in women (N=12) compared to men (N=12). However, clearances adjusted for body weight were comparable. (b) (4) (b) (4)
12.3	**Special Populations** ***Renal Impairment*** Dosage should be reduced in patients with impaired renal function receiving levetiracetam; immediate-release levetiracetam should be given to patients on dialysis [*see Dosage and Administration (2.1)*].	**Special Populations** (b) (4)

OCP requested that the sponsor provide additional analysis to support the proposed labeling changes for gender in Section 12.3 based on clearance adjusted for body weight, e.g. Day 1, Day 2 and steady state C_{max} and AUC of levetiracetam for male vs. female subjects in Study PKD_14_049. The results of this analysis are summarized below.

Evaluation of clearance adjusted by body weight using two sample t-test
Clearance adjusted for body weight was calculated for male and female subjects. Mean value of male and female subjects were compared at 5% level of significance (α=0.05).

	N	Mean	P-value	Result
Male	19	1.22	0.074	No significant difference
Female	15	1.07		

Therefore, the sponsor's proposed changes for gender in Sect. 12.3 are not acceptable.
The following changes (in blue) are recommended:

Gender
When given in a single dose, extended-release levetiracetam Cmax was 21 to 30% higher and AUC was 8 to 18% higher in women (N=12) compared to men (N=12). However, clearances adjusted for body weight were comparable. Similar results were observed in a multiple dose study for ELEPSIA XR and KEPPRA XR*.

The most current labeling approved for the reference product now includes information on the PK profile in adolescents aged 13 to 16 years treated with Keppra XR®. Given the demonstration of bioequivalence, this information is also pertinent to Levetiracetam ER Tablets and will be included in the Clinical Pharmacology section of the proposed labeling.

2.4 EXTRINSIC FACTORS

In the most recent literature search, the sponsor identified two case reports that describe a pharmacokinetic drug interaction in which concentrations of methotrexate were increased, attributed by one of the authors to possible competition for renal tubular section (a known mechanism for other reported drug interactions with methotrexate). Renal tubular secretion is one of the primary pathways of elimination of levetiracetam and, as described in the label, it has been shown that a renal tubular secretion blocking agent (probenecid) results in higher concentrations of the primary metabolite of levetiracetam; the effect of levetiracetam on other drugs has not been formally studied. While the interactions could be plausibly attributed to levetiracetam, the sponsor considers these case reports not to be a sufficiently strong basis upon which to propose a labeling change at this time.

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 XR label). The effect of alcohol on the in vitro dissolution of Levetiracetam ERTablets was studied using USP Apparatus III at 10 dpm. As dissolution has been shown to be pH independent, 0.1 N hydrochloric acid (HCl) was chosen as the medium. As requested by the Division, frequent sampling time points were added during the first 2 hours of the experiments (every 15 minutes). When 12 tablets of each strength were tested in concentrations of alcohol up to (b) (4)%, there was no effect on dissolution. Results are illustrated in the figure below.

Source: LVTER/AMR/14.0
[1] Batch used in pivotal relative bioavailability studies

During the review of the original NDA, the Division was concerned about the effect on the high-strength tablet. The sponsor submitted publications in support as well as additional data from *in vitro* dissolution studies with alcohol under various more appropriate conditions (Response to dose dumping concern; dated 23 Feb 2013). The ONDQA reviewer concurred that an *in vivo* alcohol interaction study is not warranted.

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

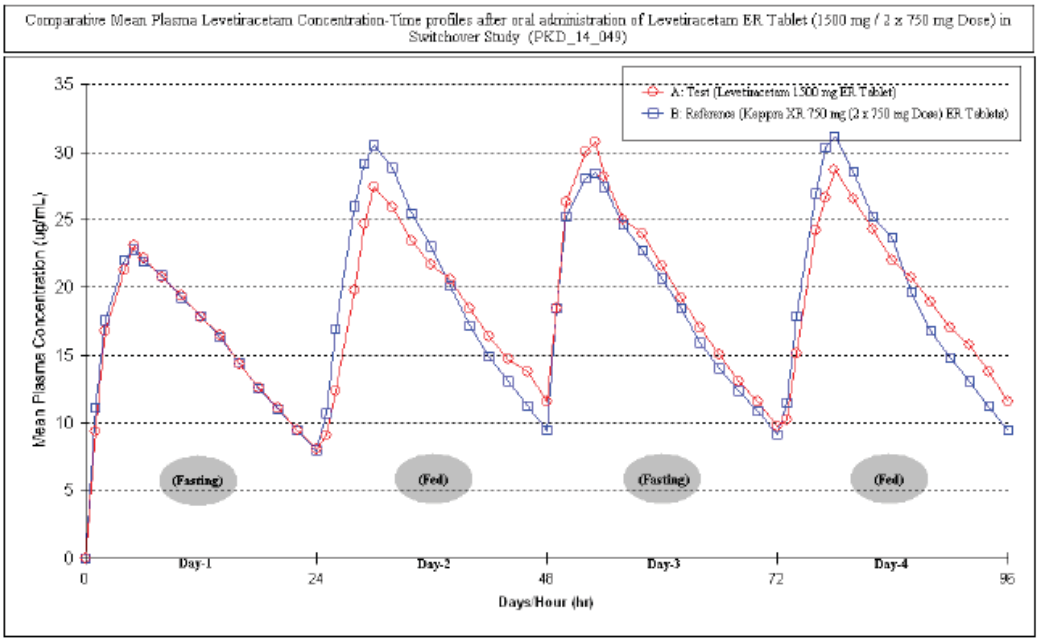
NA

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?

Levetiracetam ER Tablets, 1500 mg were bioequivalent to Keppra XR® tablets, 2 x 750 mg in the fasted and fed states. The mean PK profiles after administration of the Test and Ref product with or witout food are presented below.

Levetiracetam mean plasma concentration – time profile

Linear plot of mean plasma concentration-time profile of Levetiracetam (After day 01 to day 04 dosing) (N = 34)



Although some subjects (about 20%) had prolonged absorption when the Test product was dosed with food, this did not result in increased individual LEV C_{max} on the following day over that of the individual C_{max} of the reference product at that particular day, see discussion under Section 2.2.5.

Therefore, the proposed Levetiracetam ER Tablets can be administered regardless of food.

2.6 ANALYTICAL

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

Levetiracetam concentrations in human plasma were quantified using a validated high performance liquid chromatographic /Tandem Mass Spectrometry method. Levetiracetam was extracted from plasma using Solid Phase Extraction (SPE).

The method met the requirements of inter- and intra-assay precision, inter- and intra-assay accuracy, sensitivity, specificity, linearity, and recovery. It was shown to be linear over the range 0.199 to 39.887 µg/mL. Analyte stability was also evaluated for bench-top (9 hours at room temperature), and freeze-thaw stability (three cycles at -20°, -35°, and -65°C). Levetiracetam was also demonstrated to be stable in plasma when stored at -20°C or at -35° or -65°C for 38 days.

The validation results from Levetiracetam bioanalytical assay are are considered acceptable and the results are presented in the table below.

Validation Parameters for Levetiracetam Bioanalytical Assay

Analyte	Levetiracetam	
Internal Standard (IS)	(b) (4)	
Limit of quantitation	LLOQ : 0.199µg/mL, ULOQ : 39.887µg/mL LLOQ : 0.200µg/mL, ULOQ : 39.685µg/mL (*)	
Relative recovery of Analyte (%)	QC Low A: 90.2%, QC Med B: 93.2%, QC High : 95.0%	
Relative recovery of IS (%)	88.4%	
Absolute recovery of Analyte (%)	QC Low A: 100.3%, QC Med B: 92.7%, QC High : 95.1%	
Absolute recovery of IS (%)	93.6%	
Standard curve concentrations (µg/mL)	0.199, 0.399, 1.994, 7.479, 9.972, 17.949, 27.422, 31.162, 39.887 0.200, 0.399, 1.997, 7.488, 9.984, 17.971, 27.455, 31.199, 39.685 (*)	
QC Concentrations (µg/mL)	Low QC A: 0.598 Low QC B: 1.793 Medium QC A : 8.964 Medium QC B : 18.924 High QC : 33.615	Low QC A: 0.599 (*) Low QC B: 1.796 (*) Medium QC A : 8.982 (*) Medium QC B : 18.962 (*) High QC : 33.682 (*)
QC Intraday precision range (%)	1.6% to 3.2%	
QC Intraday Nominal range (%)	97.7% to 108.0%	
QC Inter day precision range (%)	1.0% to 3.9%	
QC Inter day Nominal range (%)	94.6% to 108.0%	
Bench-top stability (hrs)	9 hours at room temperature (in Plasma)	
	2 hours at room temperature (in Blood)	
Stock solution stability (days)	7 days at 2-8^{0}C	
Post-Processed stability (hrs)	57 hours @ 6°C	
Post Extraction Bench Top Stability	7 hours at room temperature	
Freeze-thaw stability (cycles)	03 cycles at -20±5°C, -35±5°C & -65±10°C	
Long term storage stability (Days)	38 days at -20±5°C, -35±5°C & -65±10°C	
Dilution Integrity	1.5-3 times ULOQ concentration (67.229µg/mL) diluted 5 folds.	
	% Nominal: 1/5th: 106.6	
	% Precision : 1/5th: 1.9	
Selectivity	No interference observed in blank plasma samples	

(*): Freshly Prepared for LT in matrix Experiment

3.0 DETAILED LABELING RECOMMENDATION

The reviewer's labeling recommendations are shown by track changes to the sponsor proposed label. These labeling changes should be incorporated in the revised label:

(b) (4)

3 Pages have been Withheld In Full as Draft Labeling Immediately Following this Page

4. Individual Study Review

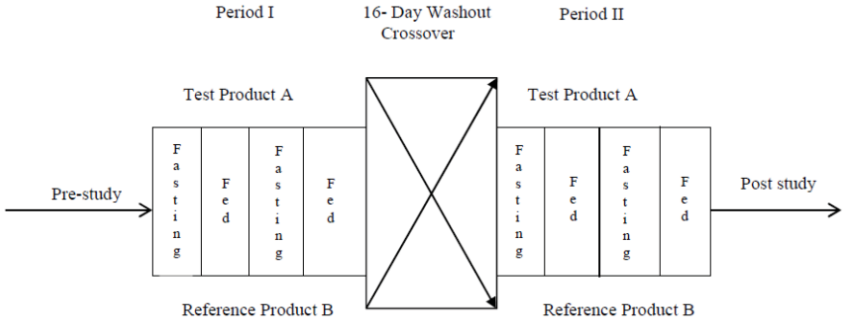
I. Study No. PKD_14_049: Randomized, Crossover, Multiple Dose, Switchover Relative Bioavailability Study of Levetiracetam 1500 mg ER Tablets

Objectives:

1. To assess the relative bioavailability between Test product (A) and Reference product (B) by means of C_{max}, AUC when switched from fasting to fed state drug administration
2. To compare the C_{min} between Test product (A) and Reference product (B) when switched from fasting to fed and fed to fasting state (all days) drug administration

Study Design	Randomized, open label, two treatment, two period, two sequence, multiple dose, crossover, switchover, relative bioavailability in which test and reference products each were given in alternating fasted and fed states (see below)*
Study Population	36 healthy subjects, 21-44 years old 34 completed: 19 men and 15 women
Treatment Group	2 groups, 2 periods, 2 sequences* Study periods were separated by a washout period of 16 days
Dosage and Administration	Treatment A (Test): one Tablet of Levetiracetam 1500 mg ER Treatment B (Reference): two Tablets of KEPPRA XR 750 mg ER Day 1 and Day 3: Single oral dose of T or R in the fasting state Day 2 and Day 4: Single oral dose of T or R, 30 min after administration of high calorie high fat breakfast
PK Sampling: plasma	At pre-dose and 1, 2, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 h postdose
Analysis	LC-MS/MS method Range: 0.20 to 40 μg/mL for Levetiracetam (LEV) See 4.1.5 for more detailed assay validation report
PK Assessment	C_{max}, t_{max}, AUC_{0-24h}, T_{max} of LEV on Day 2 and Day 4 C_{min} of LEV on Day 1, Day 2, Day 3 and Day 4
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry
PD Assessment	None

*

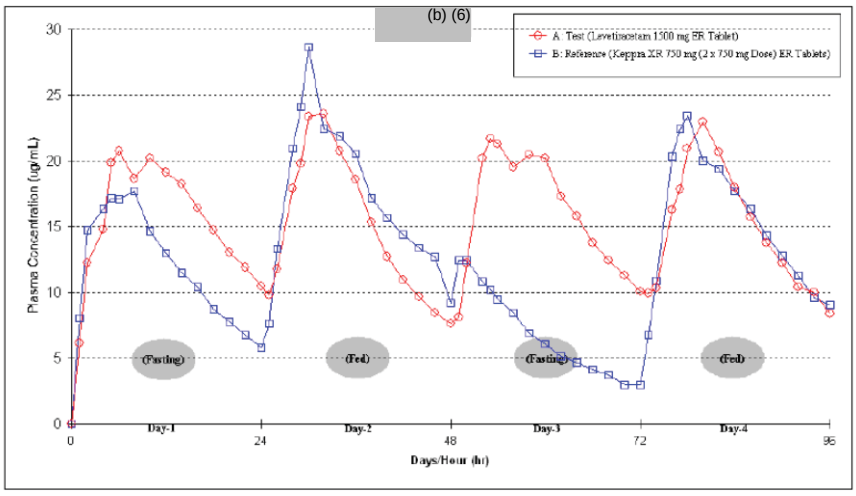


Bioanalytical Assay:
Levetiracetam concentrations in human plasma were quantified using a validated high performance liquid chromatographic/Tandem Mass Spectrometry method (LC/MS-MS). Levetiracetam was extracted from plasma using Solid Phase Extraction (SPE).
The method validation (for details, see Bioanalytical Validation Report MV_LVT_016B) and the performance of the assay during the analysis of the plasma samples were acceptable.

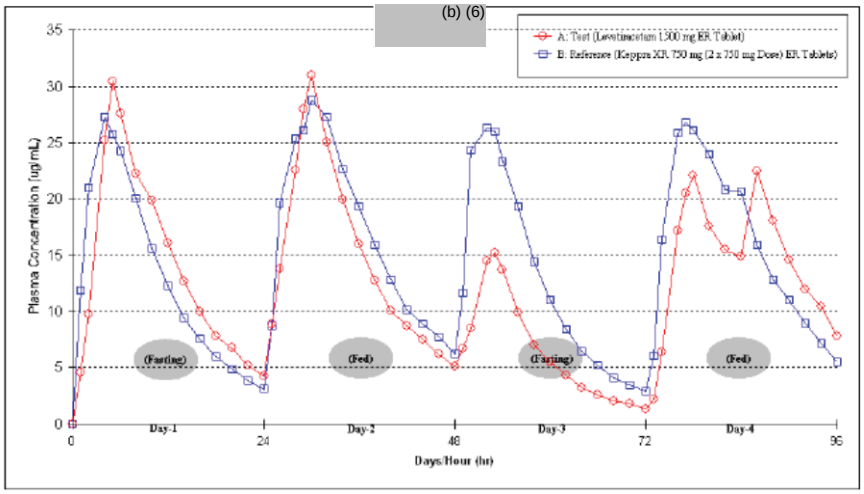
Pharmacokinetic Results:
Of the dosed 36 subjects, 34 subjects completed both periods of the study. Subject (b) (6) dropped due to incomplete meal consumption for Day 2 in period 2. Subject No (b) (6) withdrew due to personal reason before dosing in period 2.
All subjects were dosed under direct observation of study physician to ensure subjects had swallowed the study medication as a whole without chewing or crushing.
The following treatments were administered:

Treatment:	Test (A)	Reference (B)
Brand Name:	NA	Keppra XR™
Generic Name	Levetiracetam	Levetiracetam
Formulation	ER Tablet	ER Tablet
Strength	1500 mg	750 mg
Product ID	Batch Number: JKM7657B	Lot Number: 82768

Compliance was also verified by measuring plasma levels of Levetiracetam (LEV) during the analytical phase of the study. Measured plasma concentration suggested potential compliance issues for Subject number (b) (6) after administration of the Ref product on Day 3, see figure below. However, C_{max} and AUC were not evaluated on Day 3 (fasting); this issue could affect the statistics for Day 3 C_{min} at 72 hours (and potentially Day 4 C_{max}).



In addition, Subject No (b) (6) had unusually low plasma levels after the Test product on Day 3, see below and the reason is unknown.



Data of the completed 34 subjects (including Subjects (b) (6)) were used for pharmacokinetic and statistical analysis.
A summary of the pharmacokinetic parameters and statistical analysis is provided in the tables below.

Summary of Levetiracetam Pharmacokinetic Results

Pharmacokinetic Parameters (N =34)								
Day after dosing	Levetiracetam 1500mg ER Tablet Test (A)				Keppra XR™ (Levetiracetam) 750 mg (2x750 mg dose) ER tablet Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-24} (µg.h/mL)								
2	448.7392	±	115.77194	25.8	471.3419	±	112.53446	23.9
4	473.5550	±	116.20887	24.5	475.9736	±	121.32978	25.5
C_{max} (µg/mL)								
2	28.8533	±	6.76426	23.4	32.0157	±	8.46419	26.4
4	30.5734	±	7.60610	24.9	32.0387	±	7.80383	24.4
T_{max} (hr)								
2	8.265	±	4.7820	57.9	6.265	±	2.0495	32.7
4	7.706	±	3.9583	51.4	6.118	±	1.2972	21.2
***T_{max} (hr)**								
2	6.00 (4.00 - 22.00)	-	-	-	6.00 (4.00 - 14.00)	-	-	-
4	6.00 (4.00 - 20.00)	-	-	-	6.00 (5.00 - 12.00)	-	-	-
C_{min} (µg/mL)								
1	8.0134	±	2.95074	36.8	7.9089	±	2.81859	35.6
2	11.6124	±	5.38287	46.4	9.4230	±	3.25196	34.5
3	9.8020	±	3.70441	37.8	9.1178	±	3.56334	39.1
4	11.5450	±	4.95630	42.9	9.4323	±	3.21620	34.1

*Median values (range) are presented.

Source: Appendix 16.2.6.1

Results of individual pharmacokinetic parameters after day 2 and day 4 dosing (i.e day on which subjects were switched from fasting to fed condition)

AUC_{0-24} After Day 2 Dosing

$LnAUC_{0-24}$	**Levetiracetam 1500 mg Extended Release tablets Test (A)**	**Keppra XR™ (Levetiracetam) 750 mg (2 x 750mg dose) Extended Release Tablets Reference (B)**
Least Squares Means	6.07	6.13
Least squares Geometric Means	434.18	458.17
Ratio of Least-Squares Geometric Means (A/B)%	94.76	
90% Geometric C.I.	91.02 to 98.67	
Intra-Subject CV %	9.83	

C_{max} After Day 2 Dosing

LnC_{max}	**Levetiracetam 1500 mg Extended Release tablets Test (A)**	**Keppra XR™ (Levetiracetam) 750 mg (2 x 750mg dose) Extended Release Tablets Reference (B)**
Least Squares Means	3.33	3.44
Least squares Geometric Means	27.95	31.09
Ratio of Least-Squares Geometric Means (A/B)%	89.88	
90% Geometric C.I.	84.96 to 95.09	
Intra-Subject CV %	13.75	

AUC_{0-24} After Day 4 Dosing

$LnAUC_{0-24}$	**Levetiracetam 1500 mg Extended Release tablets Test (A)**	**Keppra XR™ (Levetiracetam) 750 mg (2 x 750mg dose) Extended Release Tablets Reference (B)**
Least Squares Means	6.13	6.13
Least squares Geometric Means	459.63	461.73
Ratio of Least-Squares Geometric Means (A/B)%	99.55	
90% Geometric C.I.	96.30 to 102.90	
Intra-Subject CV %	8.06	

C_{max} After Day 4 Dosing

LnC_{max}	**Levetiracetam 1500 mg Extended Release tablets Test (A)**	**Keppra XR™ (Levetiracetam) 750 mg (2 x 750mg dose) Extended Release Tablets Reference (B)**
Least Squares Means	3.39	3.44
Least squares Geometric Means	29.59	31.14
Ratio of Least-Squares Geometric Means (A/B)%	95.04	
90% Geometric C.I.	91.75 to 98.44	
Intra-Subject CV %	8.57	

Tmax

After Day 2 dosing, mean values (%CV) for the Tmax were 8.265 hour (57.9 %) for Treatment A and 6.265 hour (32.7 %) for Treatment B.

After Day 4 dosing, mean values (%CV) for the Tmax were 7.706 hour (51.4 %) for Treatment A and 6.118 hour (21.2 %) for Treatment B.

The plasma concentration at the end of dosing interval: C_{min}

After Day 1 dosing

LnC_{min}	Levetiracetam 1500 mg Extended Release tablets Test (A)	Keppra XR™ (Levetiracetam) 750 mg (2 x 750mg dose) Extended Release Tablets Reference (B)
Least Squares Means	2.02	2.00
Least squares Geometric Means	7.52	7.37
Ratio of Least-Squares Geometric Means (A/B)%	102.01	
90% Geometric C.I.	92.13 to 112.96	
Intra-Subject CV %	25.15	

After Day 2 dosing

LnC_{min}	Levetiracetam 1500 mg Extended Release tablets Test (A)	Keppra XR™ (Levetiracetam) 750 mg (2 x 750mg dose) Extended Release Tablets Reference (B)
Least Squares Means	2.36	2.19
Least squares Geometric Means	10.63	8.92
Ratio of Least-Squares Geometric Means (A/B)%	119.21	
90% Geometric C.I.	109.80 to 129.43	
Intra-Subject CV %	20.18	

After Day 3 dosing

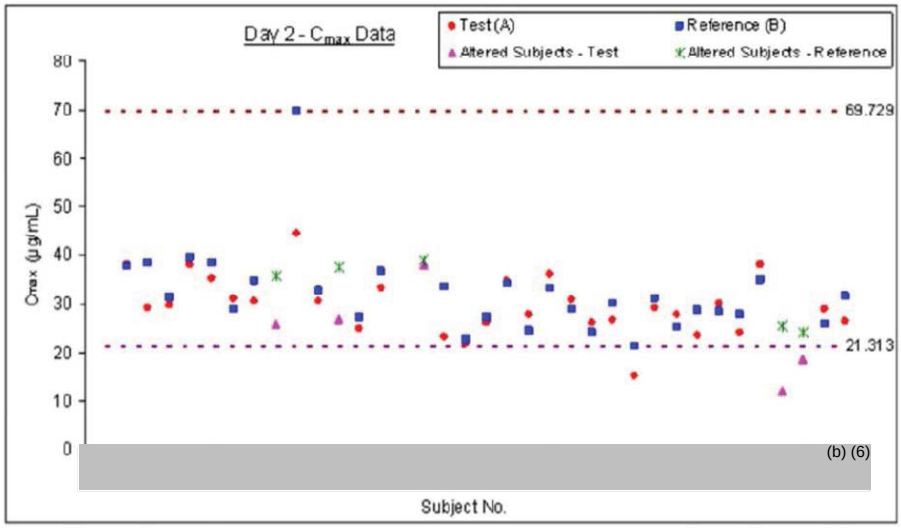
LnC_{min}	Levetiracetam 1500 mg Extended Release tablets Test (A)	Keppra XR™ (Levetiracetam) 750 mg (2 x 750mg dose) Extended Release Tablets Reference (B)
Least Squares Means	2.19	2.12
Least squares Geometric Means	8.90	8.35
Ratio of Least-Squares Geometric Means (A/B)%	106.67	
90% Geometric C.I.	94.94 to 119.85	
Intra-Subject CV %	28.89	

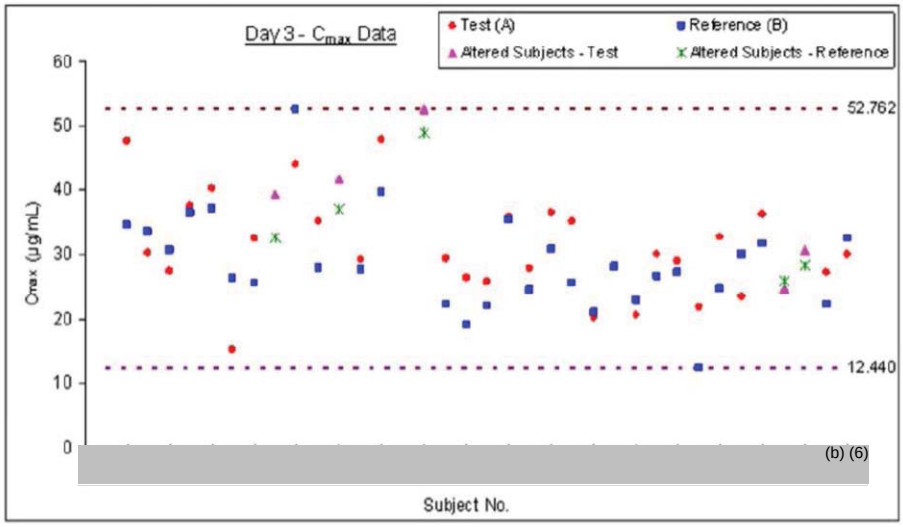
After Day 4 dosing

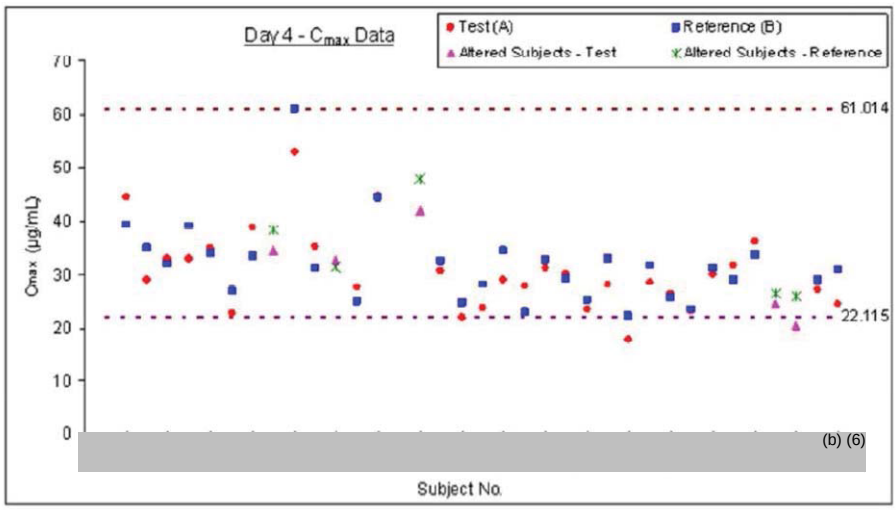
LnC_{min}	Levetiracetam 1500 mg Extended Release tablets Test (A)	Keppra XR™ (Levetiracetam) 750 mg (2 x 750mg dose) Extended Release Tablets Reference (B)
Least Squares Means	2.37	2.19
Least squares Geometric Means	10.68	8.97
Ratio of Least-Squares Geometric Means (A/B)%	119.05	
90% Geometric C.I.	109.84 to 129.02	
Intra-Subject CV %	19.75	

Note: For 3 subjects C_{min} values fell before 24 hour post dose but after C_{max} [subject No (b) (6) showed C_{min} value at 12 hour for test and 22 hour for reference treatment, subject No (b) (6) at 16 hour for test and subject No (b) (6) at 22 hour for reference treatment].

Reviewer's Comments:
The sponsor identified 5 subjects with altered PK profiles (prolonged pattern of release) following administration of the Test Extended Release Tablets with food: Subjects No (b) (6) (b) (6). In addition to these subjects, the reviewer identified two more subjects with altered PK profiles: Subject No (b) (6) and Subject No (b) (6) Subject No (b) (6) had altered PK profile in both the fed and fasted state. In two cases (Subjects No (b) (6)) this led to increased LEV C_{max} on the following day. However, this did not result in increased individual LEV C_{max} on the following day over that of the individual C_{max} of the reference product at that particular day, see scatterplots below.

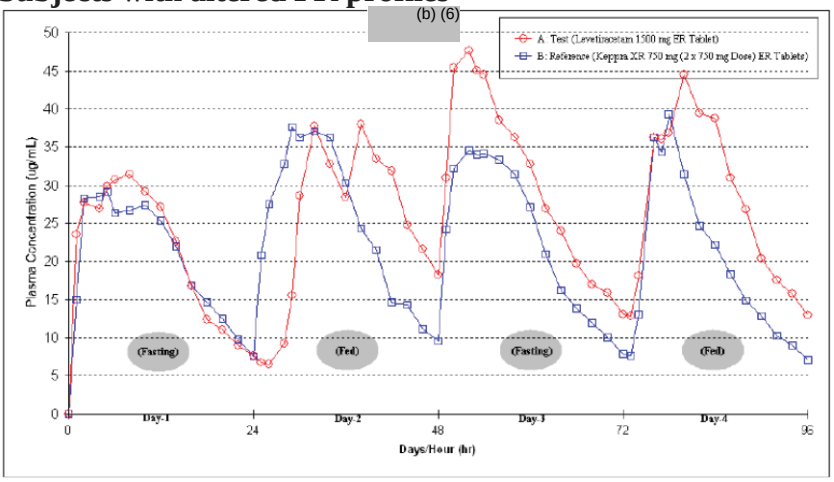


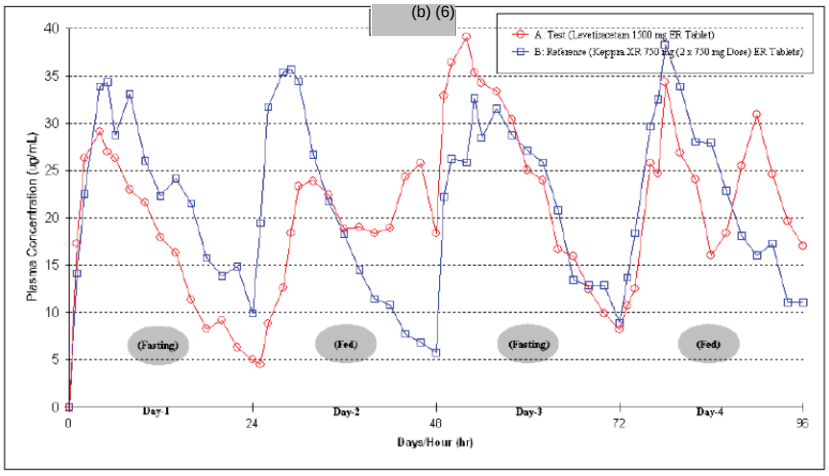


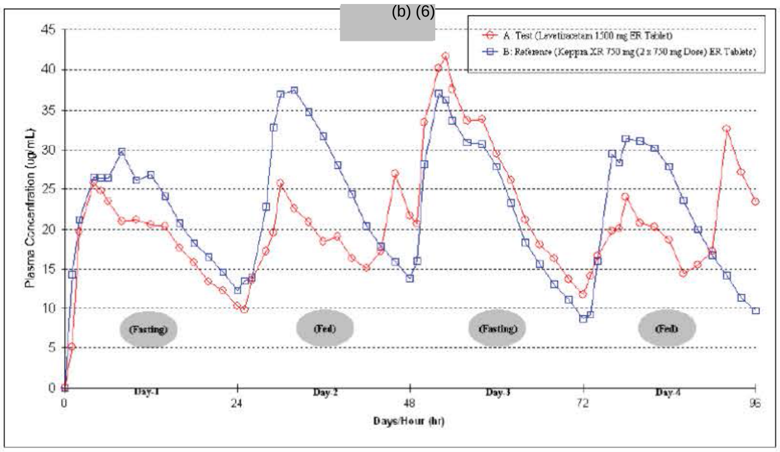


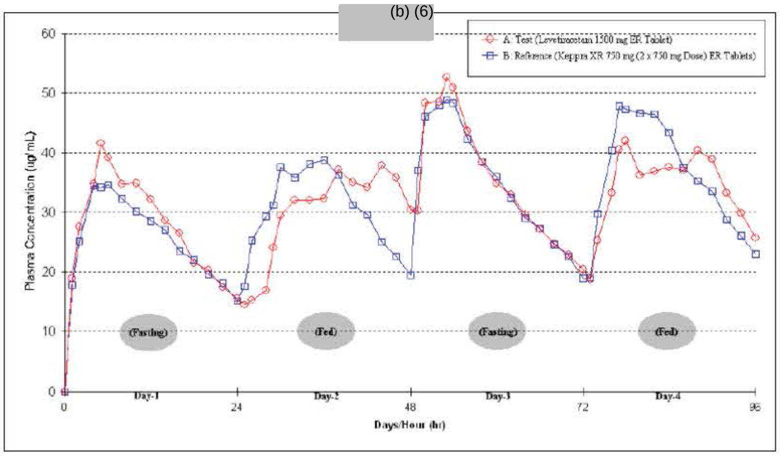
Note: Dashed line in scatterplot represents minimum and maximum value of reference product for C_{max} at particular day.

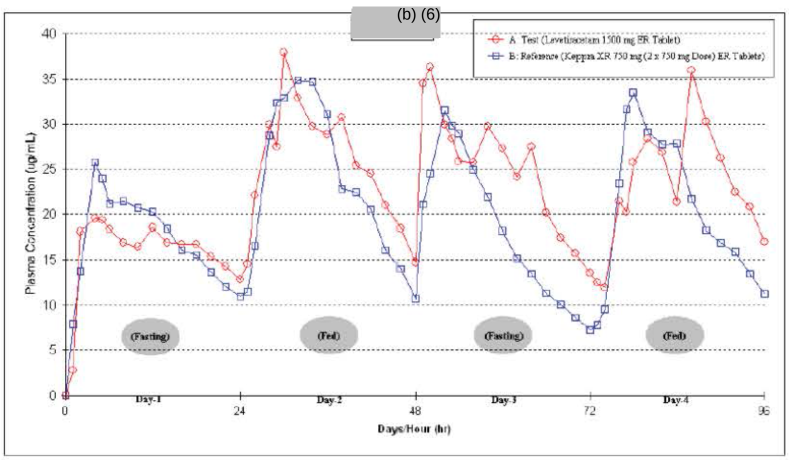
Subjects with altered PK profiles

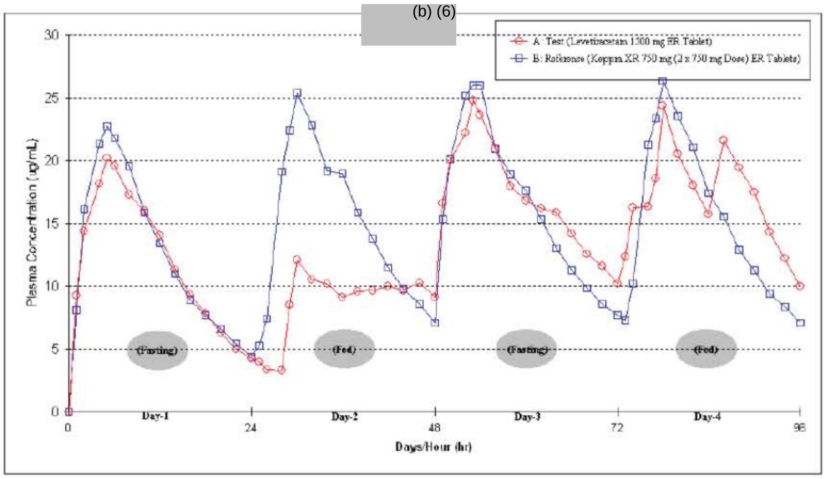


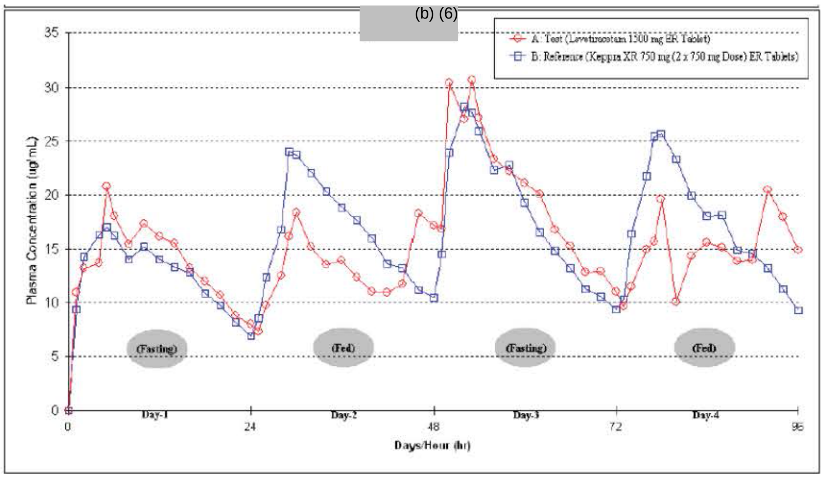


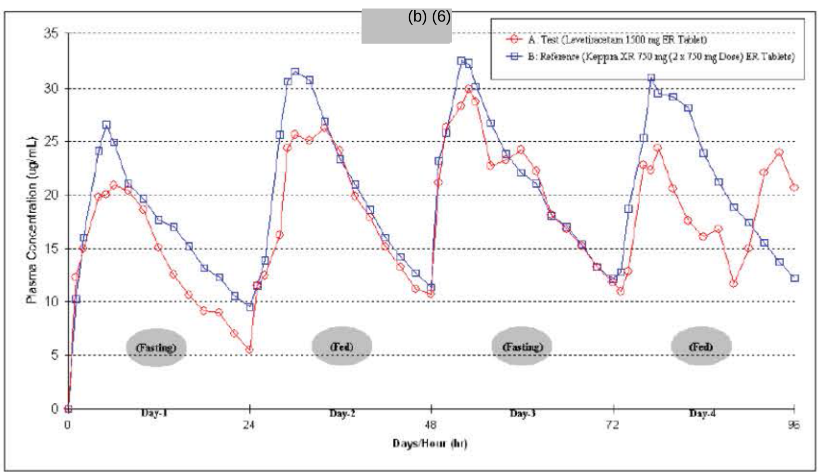

(b) (6)
A: Test (Levetiracetam 1500 mg ER Tablet)
B: Reference (Keppra XR 750 mg (2 x 750 mg Dose) ER Tablets)
Plasma Concentration (ug/mL)
(Fasting)
(Fed)
(Fasting)
(Fed)
Day-1
Day-2
Day-3
Day-4
Days/Hour (hr)


(b) (6)
A: Test (Levetiracetam 1500 mg ER Tablet)
B: Reference (Keppra XR 750 mg (2 x 750 mg Dose) ER Tablets)
Plasma Concentration (ug/mL)
(Fasting)
(Fed)
(Fasting)
(Fed)
Day-1
Day-2
Day-3
Day-4
Days/Hour (hr)

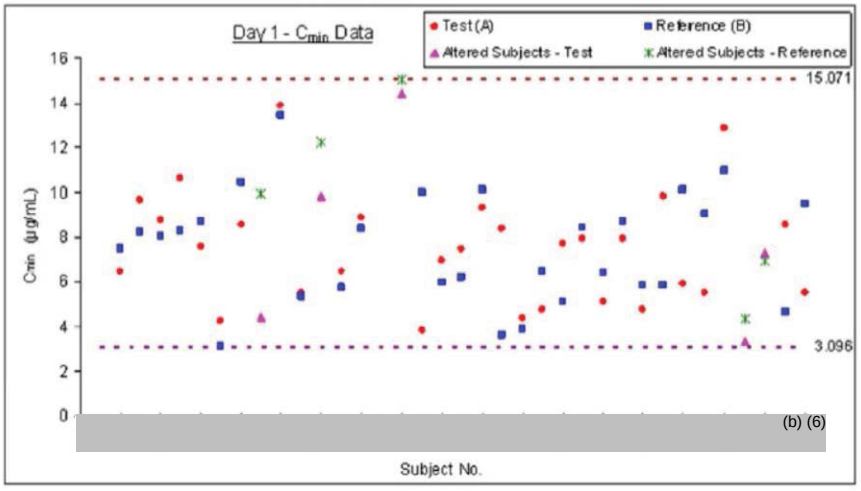

(b) (6)
A: Test (Levetiracetam 1500 mg ER Tablet)
B: Reference (Keppra XR 750 mg (2 x 750 mg Dose) ER Tablets)
Plasma Concentration (ug/mL)
(Fasting)
(Fed)
(Fasting)
(Fed)
Day-1
Day-2
Day-3
Day-4
Days/Hour (hr)

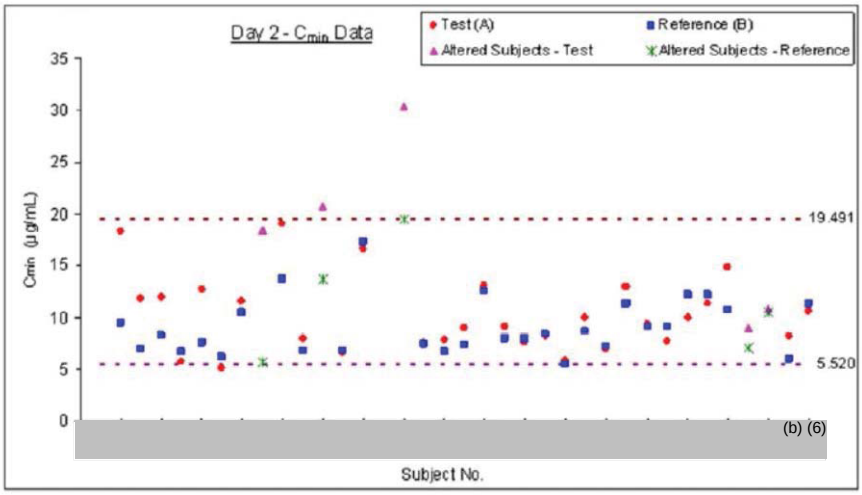

(b) (6)
A: Test (Levetiracetam 1500 mg ER Tablet)
B: Reference (Keppra XR 750 mg (2 x 750 mg Dose) ER Tablets)
Plasma Concentration (ug/mL)
(Fasting)
(Fed)
(Fasting)
(Fed)
Day-1
Day-2
Day-3
Day-4
Days/Hour (hr)

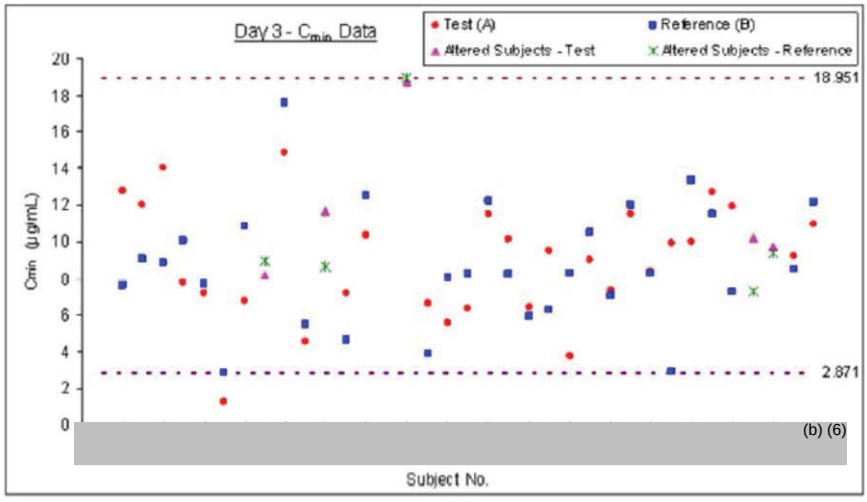

(b) (6)
A: Test (Levetiracetam 1500 mg ER Tablet)
B: Reference (Keppra XR 750 mg (2 x 750 mg Dose) ER Tablets)
Plasma Concentration (ug/mL)
(Fasting)
(Fed)
(Fasting)
(Fed)
Day-1
Day-2
Day-3
Day-4
Days/Hour (hr)


(b) (6)
A: Test (Levetiracetam 1500 mg ER Tablet)
B: Reference (Keppra XR 750 mg (2 x 750 mg Dose) ER Tablets)
Plasma Concentration (ug/mL)
(Fasting)
(Fed)
(Fasting)
(Fed)
Day-1
Day-2
Day-3
Day-4
Days/Hour (hr)

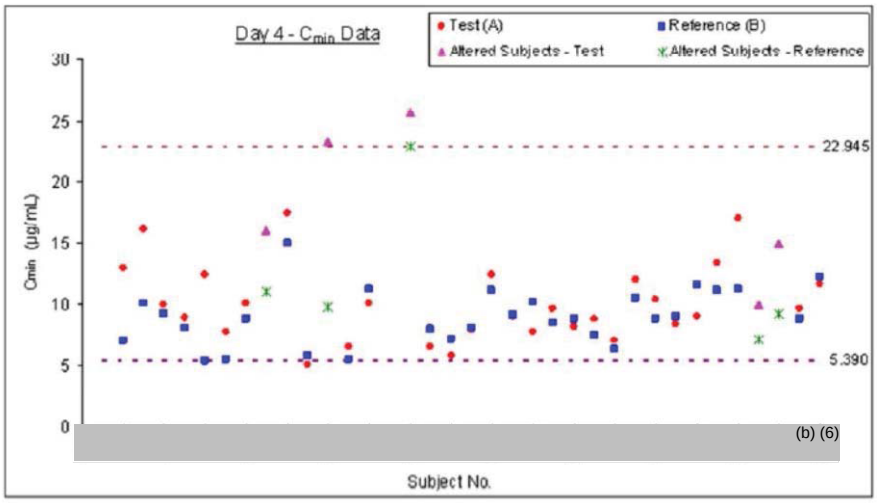
In addition, the C_{min} of the Test formulation were not below that of the Ref on any of the dosing days, see below. Therefore, there should be no decrease in efficacy when a subject is switched from Ref to Test.







Note: The only Cmin below the dashed line (minimum and maximum value of reference product at particular day) belongs to Subject number (b) (6), who had compliance issues, see page 2.



Additional statistical analysis excluding data of subject number (b) (6) was performed to evaluate the impact of its unusual PK profile observed for day 3 on overall results of the study. The results are presented below:

TABLE – 1 (Excluding data of subject number 29)								
SUMMARY OF STATISTICAL ANALYSIS LEVETIRACETAM (N =33)								
Ln- Transformed Data								
PK Variables	Least Squares Means		Least Squares Geometric Means[3]		Ratio of Least-Squares Geometric Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV%	p-value[4]
	Test	Reference	Test	Reference				
AUC_{0-24}								
Day 2	6.08	6.13	436.57	458.87	95.14	91.30 to 99.15	9.87	0.0492
Day 4	6.14	6.14	462.46	464.29	99.61	96.25 to 103.08	8.18	0.8460
C_{max}								
Day 2	3.34	3.44	28.09	31.13	90.21	85.13 to 95.59	13.90	0.0051
Day 4	3.39	3.45	29.77	31.36	94.92	91.53 to 98.44	8.69	0.0212
C_{min}								
Day 1	2.01	2.00	7.45	7.41	100.52	90.71 to 111.38	24.86	0.9328
Day 2	2.37	2.18	10.74	8.88	120.94	111.45 to 131.24	19.68	0.0004
Day 3	2.18	2.15	8.85	8.60	102.88	92.65 to114.24	25.39	0.6491
Day 4	2.38	2.19	10.77	8.95	120.38	110.98 to 130.57	19.57	0.0005

Note: The sponsor provided additional analysis to support the proposed labeling changes for gender in Section 12.3 based on clearance adjusted for body weight, e.g. Day 1, Day 2 and steady state C_{max} and AUC of levetiracetam for male vs. female subjects in Study PKD_14_049. The results of this analysis are summarized below.

Evaluation of clearance adjusted by body weight using two sample t-test

Clearance adjusted for body weight was calculated for male and female subjects. Mean value of male and female subjects were compared at 5% level of significance (α=0.05). No significant gender difference was observed.

	N	Mean	P-value	Result
Male	19	1.22	0.074	No significant difference
Female	15	1.07		

TABLE –5A1								
SUMMARY OF RESULTS								
LEVETIRACETAM (FEMALE, N =15)								
Pharmacokinetic Parameters								
Day after dosing	Levetiracetam 1500mg ER Tablet Test (A)				Keppra XR™ (Levetiracetam) 750 mg (2x750 mg dose) ER tablet Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-24} (µg.h/mL)								
1	438.8645	±	114.18110	26.0	447.9325	±	103.90891	23.2
2	503.8184	±	123.09891	24.4	535.0099	±	121.52837	22.7
4	534.6855	±	135.68229	25.4	528.1251	±	155.22681	29.4
C_{max} (µg/mL)								
1	28.5581	±	6.05956	21.2	29.4650	±	5.63923	19.1
2	31.9041	±	5.86571	18.4	37.3533	±	9.70190	26.0
4	35.6955	±	7.77407	21.8	36.7289	±	9.06812	24.7

Source: Appendix 16.2.6.6

TABLE –5A2								
SUMMARY OF RESULTS								
LEVETIRACETAM (MALE, N =19)								
Pharmacokinetic Parameters								
Day after dosing	Levetiracetam 1500mg ER Tablet Test (A)				Keppra XR™ (Levetiracetam) 750 mg (2x750 mg dose) ER tablet Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-24} (µg.h/mL)								
1	324.3583	±	50.34215	15.5	321.6715	±	58.50329	18.2
2	405.2556	±	90.89844	22.4	421.0777	±	75.40136	17.9
4	425.2941	±	69.76378	16.4	434.8014	±	64.74339	14.9
C_{max} (µg/mL)								
1	20.3728	±	3.31072	16.3	19.6386	±	4.14025	21.1
2	26.4448	±	6.57605	24.9	27.8018	±	3.95606	14.2
4	26.5296	±	4.46470	16.8	28.3360	±	3.85866	13.6

Source: Appendix 16.2.6.6

PK Conclusions:
Seven out of 34 subjects (20%) had a "prolonged pattern of release" following administration of the Test Extended Release Tablets with food, one of these subjects had altered PK profile in the fasted state as well. However, this did not result either in potentially sub-therapeutic concentrations nor higher peak concentrations than that of the reference product when subjects were dosed the following day.
In addition, the ratios of the least-square means (and 90% confidence intervals) of the Test to Reference product (A/B) for LEV after day 2 and day 4 of dosing were within the BE limits: 94.76% (91.02 to 98.67) and 99.55% (96.30 to 102.90), respectively for AUC_{0-24}; 89.88% (84.96 to 95.09) and 95.04% (91.75 to 98.44), respectively for C_{max}. The slight increases in C_{min} above the BA limits [the ratios of the least-square means (and 90% CI) of the Test to Reference product (A/B) for LEV after day 1 to day 4 of dosing were 102.01% (92.13 to 112.96), 119.21% (109.80 to 129.43), 106.67% (94.94 to 119.85) and 119.05% (109.84 to 129.02) respectively] are not expected to have a clinically meaningful effect.
There was no significant difference in clearance adjusted for body weight between male and female subjects.

Safety
No death or serious adverse events occurred during the study. Of the observed 6 adverse events, 3 adverse events were experienced by 2 subjects when received treatment A. One adverse event was experienced by 1 subject when received treatment B. The remaining two adverse events which were considered to be emerged from both the formulations occurred in one subject. Two subjects reported a moderate headache, one following dosing with the test product and one following dosing with the reference product; these were judged unlikely related to treatment. The other events occurring in single subjects following dosing with the test product; one was mild giddiness, judged possibly treatment related, and one was pruritus, judged unlikely related. Post study significant laboratory abnormalities were observed for subject number (b) (6) and were reported as adverse events. Since no biochemistry assessment was done after screening until check out of period 2, these adverse events were considered to have emerged from both the treatments.

Bioanalytical Validation Report MV_LVT_016B

Levetiracetam concentrations in human plasma from Study PKD_14_049 (Randomized, Crossover, Multiple Dose, Switchover Relative Bioavailability Study of Levetiracetam 1500 mg ER) were quantified using a validated high performance liquid chromatographic /Tandem Mass Spectrometry method (LCMS/MS) method. Levetiracetam and its internal standard, (b) (4), were extracted from plasma (containing K_2EDTA anticoagulant) by solid-phase extraction prior to LC-MS/MS analysis. Concentrations of levetiracetam were determined by linear regression with a weighting factor of $1/x^2$. The lower limit of quantitation was evaluated by comparing the peak responses (area) of eight extracted samples of the lowest calibration standard (CS1) spiked in eight different blank matrices to the peak responses of eight respective blank matrix sample. There was no significant interference observed in Blank Plasma. The validation results are summarized in the table below.

Analyte	Levetiracetam	
Internal Standard (IS)	(b) (4)	
Limit of quantitation	LLOQ : 0.199µg/mL, ULOQ : 39.887µg/mL LLOQ : 0.200µg/mL, ULOQ : 39.685µg/mL (*)	
Relative recovery of Analyte (%)	QC Low A: 90.2%, QC Med B: 93.2%, QC High : 95.0%	
Relative recovery of IS (%)	88.4%	
Absolute recovery of Analyte (%)	QC Low A: 100.3%, QC Med B: 92.7%, QC High : 95.1%	
Absolute recovery of IS (%)	93.6%	
Standard curve concentrations (µg/mL)	0.199, 0.399, 1.994, 7.479, 9.972, 17.949, 27.422, 31.162, 39.887 0.200, 0.399, 1.997, 7.488, 9.984, 17.971, 27.455, 31.199, 39.685 (*)	
QC Concentrations (µg/mL)	Low QC A: 0.598 Low QC B: 1.793 Medium QC A : 8.964 Medium QC B : 18.924 High QC : 33.615	Low QC A: 0.599 (*) Low QC B: 1.796 (*) Medium QC A : 8.982 (*) Medium QC B : 18.962 (*) High QC : 33.682 (*)
QC Intraday precision range (%)	1.6% to 3.2%	
QC Intraday Nominal range (%)	97.7% to 108.0%	
QC Inter day precision range (%)	1.0% to 3.9%	
QC Inter day Nominal range (%)	94.6% to 108.0%	
Bench-top stability (hrs)	9 hours at room temperature (in Plasma)	
	2 hours at room temperature (in Blood)	
Stock solution stability (days)	7 days at 2-8^{0}C	
Post-Processed stability (hrs)	57 hours @ 6°C	
Post Extraction Bench Top Stability	7 hours at room temperature	
Freeze-thaw stability (cycles)	03 cycles at -20±5°C, -35±5°C & -65±10°C	
Long term storage stability (Days)	38 days at -20±5°C, -35±5°C & -65±10°C	
Dilution Integrity	1.5-3 times ULOQ concentration (67.229µg/mL) diluted 5 folds.	
	% Nominal: 1/5th: 106.6	
	% Precision : 1/5th: 1.9	
Selectivity	No interference observed in blank plasma samples	

(*): Freshly Prepared for LT in matrix Experiment

The method met the requirements of inter- and intra-assay precision, inter- and intra-assay accuracy, sensitivity, specificity, linearity, and recovery. It was shown to be linear over the range 0.199 to 39.887 µg/mL. Analyte stability was also evaluated for bench-top (9 hours at room temperature), and freeze-thaw stability (three cycles at -20°, -35°, and -65°C). Levetiracetam was also demonstrated to be stable in plasma when stored at -20°C or at -35° or -65°C for 38 days.

This method is similar to that used in the analysis of the pivotal studies (PKD_10_130, PKD_10_131 and PKD_10_272) included in the original NDA. Some changes to the analytical method have been made with respect to instrument sensitivity. These do not affect the interpretation of the results. The table below provides a comparison of the important assay parameters for the previous studies and the current study.

Overview of Original Bioanalytical Method (ATP_02_LVT) and Current Method Used for "Switching" Study (ATP_03_LVT and ATP_04_LVT)

	Original Studies	"Switch Over" Study No. PKD_14_049	
ATP No.	ATP_02_LVT	ATP_03_LVT	ATP_04_LVT
Method Validation No.	MV_LVT_016A	MV_LVT_016B	MV_LVT_016B
Anti-coagulant	K_2 EDTA		
Extraction Type	SPE		
Mobile Phase	Methanol:Acetonitrile (80:20) : 2 mm Ammonium acetate; pH:3.4 (90:10)		
Column	Symmetry C18, 75×4.6 mm, 3.5 µ		
Injection Volume	2 µL		
Range	0.220 - 39.984 µg/mL	0.199 - 39.887 µg/mL	
Diluent	45:55(methanol:water)	40:60 (methanol:water)	
Flow Rate	0.650 mL/min	1.0 mL/min (splitter)	
Auto Sampler Temperature	10°C	6°C	
Instrument	API-2000 and Shimadzu HPLC	API-4000 and Dionex UHPLC	
Run Time (minutes)	2.5	2.0	

Note: A Pre-Approval Data Validation Inspection was requested on Sept 26, 2014.
On Oct 21, 2014 the Division of Bioequivalence and GLP Compliance Office of Scientific Investigations recommended accepting data for NDA 204417 without on-site inspection of the clinical and bioanalytical sites based on the satisfactory inspections in recent years and the similarity of the methodologies and processes in the previous submission [studies PKD_10_130 (Fasted) & PKD_10_272 (Fed)], which were inspected by the Division in 2013.

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/s/

HRISTINA DIMOVA
01/21/2015

YUXIN MEN
01/22/2015

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 204417
End of Review
Sponsor: Sun Pharma Advanced Research Company, Ltd.
Drug: Levetiracetam Extended Release (1000 and 1500 mg)
Formulation: Extended Release Tablets
Indication: Adjunctive therapy in the treatment of partial onset seizures in patients ≥ (b) (4) years of age with epilepsy
Submission Date: July 17, 2013
Internal Meeting Date: Sept 24, 2013
Sponsor Meeting Date: Oct 07, 2013
Reviewer: Hristina Dimova, Ph.D.
Team Leader: Angela Men, M.D., Ph.D.

1. Background
The sponsor submitted an NDA (204417) for Levetiracetam Extended Release Tablets (1000mg and 1500mg) as adjunctive therapy in the treatment of partial onset seizures in patients ≥ (b) (4) years of age with epilepsy.
The sponsor wants to discuss the studies necessary for a Complete Response to the issues outlined in the Division's Complete Response letter dated 29 Mach 2013.

2. LIST OF SPECIFIC ISSUES AND QUESTIONS GROUPED BY DISCIPLINE
The issues for discussion, pertaining to Clinical Pharmacology and the safety and efficacy implications, are presented below. The Division's concern is presented verbatim (in italics), followed by SPARC Ltd.'s response and proposed study(ies).

Food Effect
We acknowledge that the data from your bioequivalence (BE) studies establish that your product is bioequivalent to Keppra XR in the fasted state. However, examination of the data from your two BE studies in the fed state (Studies 131 and 272) reveals that a substantial percent of patients have plasma concentration-time curves that differ significantly between your product and Keppra XR, despite the observation that in Study 272, your product meets bioequivalence criteria for Cmax and A UC. As you know, the Division considers similarity of the overall shapes of these curves to be an important factor in deciding that two products will have similar safety and effectiveness.
SPARC Ltd.'s Response: Twelve of 40 subjects (30.0%) had altered plasma concentration profiles across the two fed studies. SP ARC Ltd. understands that the Division is concerned about the overall shape of the plasma concentration profile of SP ARC Ltd. product when given with food, despite demonstration of bioequivalence in the pivotal fed study (PKD_10_272). The simulations submitted during review of NDA were not sufficient to demonstrate the similarity of plasma concentration profile curve of SPARCL Ltd product with that of Keppra XR®.
Therefore, SPARC Ltd. proposes to conduct additional studies to further understand the pharmacokinetics of the proposed Levetiracetam Extended Release Tablets. An overview of the studies is provided below. These studies will provide data beginning with the first

dose and continuing to steady state under varying dosing conditions. With these additional studies, the total exposure to the 1500-mg tablet will be approximately 100-130 subjects, providing a better estimate of the incidence of subjects with altered profiles. In addition, repeated dosing will allow an evaluation of whether or not the effect is consistent within a subject.

STEADY STATE SWITCH OVER STUDIES

SPARC Ltd. propose to conduct two fasted-fed I fed-fasted (switch over) steady state studies of SPARC Ltd.'s Levetiracetam Extended Release Tablets (test) with KeppraXR® tablets (reference). The objective of these studies is to compare the exposure to drug during the initial days of dosing as well as the shape of the steady-state plasma concentration profile curves of SPARC Ltd.'s Levetiracetam ER tablets (test) against Keppra XR® (reference). An overview of these studies is provided below.

For each, the study design will be randomized, open-label, two treatments, two periods, two sequences, multiple dose, and crossover steady state study, when dosed under fasted and fed conditions on alternate days.

In each of the two study periods, either test or reference product will be orally administered under fasted or fed conditions (please refer to Tables 1 and 2) for 4 successive days as per randomization schedule.

Details of these studies are given below.

STUDY 1: STEADY STATE SWITCH OVER STUDY FOR PLASMA CONCENTRATION CURVE COMPARISON IN FED STATE

In each of the two study periods, pre-dose blood samples will be collected at Day 1 (Dose 1), Day 2 (Dose 2), Day 3 (Dose 3) and Day 4 (Dose 4). On the days of dosing with food, post-dose blood samples will be collected to assess the concentration-time curve.

The shape of plasma concentration profile curves obtained from test will be compared with that of reference. As secondary objectives, Cmax, AUC (fed days only), and Cmin (all days) will be compared using the two one-tailed confidence interval approach.

The study will be initiated by dosing test or reference product under fasted conditions and dosing will be continued till 4th day. Refer to Table 1 for dosing schedule.

Table 1: Dosing schedule of study 1 for test and reference product

Product	Day 1	Day 2	Day 3	Day 4
Reference	Fasted	Fed	Fasted	Fed
Test	Fasted	Fed	Fasted	Fed

STUDY 2: STEADY STATE SWITCH OVER STUDY FOR PLASMA CONCENTRATION CURVE COMPARISON IN FASTED STATE

In each of the two study periods, pre-dose blood samples will be collected at Day 1 (Dose 1), Day 2 (Dose 2), Day 3 (Dose 3) and Day 4 (Dose 4). On the 4th day of dosing with fasted, post-dose blood samples will be collected to assess the concentration-time curve.

The shape of plasma concentration profile curves obtained from test will be compared with that of reference. As secondary objectives, Cmax, AUC (fasted Day 4 only), and Cmin (all days) will be compared using the two one-tailed confidence interval approach.

The study will be initiated by dosing test or reference under fed conditions and dosing will be continued until the 4th day. Refer to Table 2 for dosing schedule.

Table 2: Dosing schedule of study 2 for test and reference product

Product	Day 1	Day 2	Day 3	Day 4
Reference	Fed	Fasted	Fed	Fasted
Test	Fed	Fasted	Fed	Fasted

Comment: Keppra XR half-live is 7 h, therefore 4 days is enough to reach steady state. However, the plasma concentrations profiles need to be evaluated after both fasted and fed conditions (Day 1, Day 2, Day 3 and Day 4) to assess what % of subjects have altered PK profiles when switched from fasted/fed or fed/fasted state. It is not clear why Study 2 is needed.
The sponsor needs to conduct only Study 1 with assessing the plasma concentrations profiles in all subjects after both fasted and fed conditions and comparing Cmax, AUC (fed days only), and Cmin (all days) using the two one-tailed confidence interval approach.

STUDY 3: FOOD EFFECT STUDY
If it would be useful for the Division's review and to allow informed labeling, SP ARC Ltd. would also agree to study the effect of meal composition on the plasma concentration profile. This study would allow a better understanding of the basis for the observed altered profile in a subset of subjects. Briefly, the study would be a single-dose crossover study of the following two dosing conditions:
• High-calorie Approximately 900 K Cal, high-fat (~50%) meal
• Standard meal (650K Cal,~ 30% from fat)

Comment: This Study (3) is not needed. Levetiracetam Extended Release (1000 and 1500 mg) label can not be different from Keppra XR (b) (4) (b) (4).

SPARC Ltd.'s Topics for Discussion:
1. Are the two proposed steady-state switchover studies and acceptance criteria appropriately designed to address the Division's concerns about dosing with food? Does the Division have any additional recommendations?

Clinical Pharmacology Preliminary Response to Question 1:
You only need to conduct Study 1. This study should assess the plasma concentration profiles in all subjects after both fasted and fed conditions and compare C_{max} and AUC (fed days only) as well as C_{min} (all days) using the two one-sided tests procedure. The plasma concentration profiles need to be evaluated after both fasted and fed conditions (Day 1, Day 2, Day 3, and Day 4) to assess what percentage of subjects have altered PK profiles when switched from fasted/fed or fed/fasted state.

2. Does the Division recommend that SPARC Ltd. conduct the single-dose, crossover, food composition study? Would the results of such a study be included in the labeling?

Clinical Pharmacology Preliminary Response to Question 2:
Study 3 is not needed.

3. Taken together, do the studies provide sufficient support for a Complete Response or are additional studies required?

Clinical Pharmacology Preliminary Response to Question 3:
Please see the responses to Questions 1 and 2.

4. If in each of the study substantial numbers of test curves have similar shape as that of reference, can the Division agree that safety and effectiveness are expected to be similar to the reference product when dosed in the fed or fasted states?

Clinical Pharmacology Preliminary Response to Question 4:
This will be a review issue.

Waiver of Lower Strength Tablets
... In addition, because we have found that the 1500 mg tablet does not perform similarly to Keppra XR, we cannot approve your 1000 mg tablet based on a waiver of the bioequivalence requirement for that strength.

SPARC Ltd.'s Response:
If data are generated to establish acceptable relative bioavailability for the 1500-mg tablet strength, SPARC Ltd. will request a waiver of the need for in vivo studies of the lower tablet strength.
If on the other hand, the higher tablet strength is found not to be bioequivalent to the reference product when given with food or is not further pursued, SPARC Ltd. Proposes to conduct a single-dose, two-way crossover relative bioavailability study in the fed state on 1000-mg strength. In each of the two study periods, either test product Levetiracetam Extended Release Tablet 1000 mg or the reference product KEPPRA XR®

(levetiracetam) 1000 mg (2 x 500 mg) Tablets will be orally administered 30 minutes after administration of a high-calorie, high-fat breakfast, as per randomization schedule. Pre-dose and post dose samples will be collected to assess the concentration-time curve. In addition to evaluating C_{max} and AUC, the individual subject plasma concentration curves will be evaluated to ensure that no subject has a prolonged absorption profile. As the 1500-mg strength has been demonstrated to be bioequivalent to the reference product in the fasted state, SPARC Ltd. does not plan to conduct a fasted relative bioavailability study.

SPARC Ltd.'s Topics for Discussion:
5. As the Division has acknowledged that SPARC Ltd.'s 1500-mg strength is bioequivalent to Keppra XR® 1500 mg (2 x 750 mg) in the fasted state, can the Division waive the bioequivalence study for 1000-mg in fasted state (even if the 1500-mg tablet strength ultimately is not approved)?
This question was addressed by ONDQA.

6. Based on this study will FDA approve the 1000-mg strength irrespective of the outcome additional studies of the 1500-mg tablet strength?

Clinical Pharmacology Preliminary Response to Question 6:
We agree that the single-dose, two-way crossover bioequivalence study in the fed state on the 1000-mg strength as described on page 5 of your submission has the potential to support approval of the 1000-mg tablet irrespective of the outcome of the additional studies of the 1500-mg tablet strength.

Alcohol "Dose Dumping"
In addition, the 1500 mg tablet showed dose dumping potential at the highest alcohol concentration (b) (4)%) in the in vitro studies. The labeling of the RLD does not have a statement limiting alcohol use. The Division is concerned that adding an alcohol use limitation to the label for your proposed ER formulation could lead to clinical consequences similar to those described above regarding fed/fasting administration. This issue, however, may potentially be resolved if you conduct an in vivo study to evaluate the impact of the observed effect in vitro.

SPARC Ltd.'s Response: Dose-dumping in media with (b) (4)% alcohol was seen when dissolution of the 1500-mg tablets was studied under the following dissolution conditions (no dose dumping was seen for the 1000-mg strength):
Apparatus: USP <724> Apparatus 3 (Reciprocating Cylinder (b) (4) (b) (4))
Medium: 0.1N HCl buffer at 37.0 ± 0.5 oc with (b) (4)% alcohol
Speed: 15 dips per minute (6 tablets)

SPARC Ltd.'s Topics for Discussion:
7. Considering these data, does the Division still recommend an in vivo alcohol interaction study for the 1500-mg strength?
This question was addressed by ONDQA.

8. Since the 1000-mg strength does not show dose dumping under any of the conditions, SPARC Ltd. requests confirmation that this lower strength tablet would be approvable regardless of the outcome of studies of the 1500-mg tablet.

Clinical Pharmacology Preliminary Response to Question 8:
Please see the responses to Questions 1, 2, 6, and 7. Ultimately, the approvability of the 1000-mg strength is a matter of review.

The face-to-face meeting was cancelled by the sponsor after receiving the FDA Preliminary Responses.

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/s/

HRISTINA DIMOVA
10/08/2013

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Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Levetiracetam Extended Release (1000 and 1500 mg)
PRODUCT (Brand Name):	NA
NDA:	204417
DOSAGE FORM:	Extended-Release Tablets
DOSAGE STRENGTH:	1000 mg and 1500 mg
INDICATION:	Adjunctive therapy in the treatment of partial onset seizures in patients ≥ (b) (4) years of age with epilepsy
NDA TYPE:	Standard
SUBMISSION DATE:	May 24, 2012
SPONSOR:	Sun Pharma Advanced Research Company, Ltd.
REVIEWER:	Hristina Dimova, Ph.D.
PHARMACOMETRICS REVIEWER/TEAM LEADER:	Atul Bhattaram, Ph.D.
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OCPB DIVISION:	DCP-I
OND DIVISION:	HFD-120

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1.0 EXECUTIVE SUMMARY

Levetiracetam, an antiepileptic drug, was first approved in 1999 as Keppra®, an immediate release tablet, and is currently approved for the following indications: adjunctive therapy of partial onset seizures; adjunctive treatment of myoclonic seizures and primary generalized tonic-clonic seizures. An extended release tablet, Keppra XR®, was later approved in 2008, indicated for adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. Two strengths of Keppra XR® are available, 500 mg and 750 mg, with the higher strength (750 mg) as the reference listed drug (RLD). 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. In order to reduce the number of tablets to be taken daily, the sponsor has developed higher strength tablets, using a proprietary technology, intended to be bioequivalent to the RLD when administered in the same total dose.

This is a 505(b)(2) NDA submission for the 1000 mg and 1500 mg strength extended-release (ER) tablets. The sponsor will rely on FDA's prior judgment of the safety and efficacy of levetiracetam for the same indication, dosing, and route of administration as described in the most current labeling for Keppra XR® as agreed with the Division in a Pre-NDA meeting held on 31 October 2011. No toxicological testing or clinical studies have been performed in support of this NDA as per Pre-NDA meeting discussion.

Levetiracetam is classified as BCS class 1 drug. The sponsor followed OGD's draft guidance for levetiracetam (extended release) conducting fasting, fed and dissolution studies. Three single-dose, randomized, open-label, crossover bioequivalence (BE) studies were conducted to compare the final proposed formulation of Levetiracetam ER Tablets, 1500 mg to the RLD, Keppra XR® Tablets (2 x 750 mg) in healthy adult subjects under fasted and fed conditions. The sponsor also conducted fasted and fed BE studies with four earlier pilot formulations of Levetiracetam ER Tablets, 1500 mg. A waiver of the need for an in vivo study of the lower strength is included, supported by the composition proportionality of the tablets and the results of multi-media in vitro dissolution testing. In vitro dissolution in alcoholic media has also been studied. Levetiracetam ER Tablets, 1500 mg were bioequivalent to Keppra XR® tablets, 2 x 750 mg in the fasted state. The first fed BE study (n=18), failed to meet BE criteria for C_{max}, the BE criteria for AUC were met. The sponsor repeated the study under fed conditions in a larger population (n=22) and omitting earlier sampling time points and adding additional time points at the later part of the plasma concentration profile; the proposed product was found to be BE to RLD. However, about one third of the subjects in the fed pivotal studies demonstrated a "prolonged pattern of release" following administration of the Test Extended Release Tablets with no clear reasons. The sponsor provided simulations suggesting that the Test and the Reference product are likely to be bioequivalent at steady state (based on AUC and Cmax). However, the sponsor's simulations demonstrated that the individual plasma concentration-time profiles after administration of the Test formulation at steady state will not be similar in shape to that of the Reference formulation. Additionally, the sponsor claims that "the range of trough

concentrations resulting in subjects with prolonged pattern of release fall within the range of observed trough concentrations of 4.6-21 μg/mL in responders at 12-hour with Keppra" based on Clinical Pharmacology and Biopharmaceutics Review (Levetiracetam KEPPRA XR). The impact of the difference in shape of the plasma concentration time curve on the efficacy of this product is not well understood. The sponsor's claim is not acceptable since the relationship between levetiracetam PK and PD profiles is not sufficiently well understood to justify approval based on trough levels. In addition, another sponsor's FDA review can not be referenced in a 505(b)(2) application.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 204417. The submission is not acceptable from a Clinical Pharmacology and Biopharmaceutics point of view for the reasons summarized below:

1) The shape of the concentration-time profiles after administration of the Test formulation Levetiracetam ER with food is different from that of RLD. Overall, about one third of the subjects in the fed pivotal studies demonstrated a "prolonged pattern of release" following administration of the Test Extended Release Tablets with no clear reasons.

The sponsor provided simulations suggesting that the Test and the Reference product are likely to be bioequivalent at steady state (based on AUC and C_{max}). However, the sponsor's simulations did not demonstrate that the individual plasma concentration-time profiles after administration of the Test formulation at steady state will be similar in shape to that of the Reference formulation. Additionally, the sponsor claims that "the range of trough concentrations resulting in subjects with prolonged pattern of release fall within the range of observed trough concentrations of 4.6-21 μg/mL in responders at 12-hour with Keppra" based on Clinical Pharmacology and Biopharmaceutics Review (Levetiracetam KEPPRA XR). This claim is not acceptable since the relationship between levetiracetam PK and PD profiles is not sufficiently well understood to justify approval based on trough levels. In addition, another sponsor's FDA review can not be referenced in a 505(b)(2) application.

In conclusion, the sponsor's simulations did not address the Division's concern about the differences in the shape of the concentration-time profiles. The claim that "there is no safety and / or efficacy risk and the SPARCL formulation is predicted to behave similar to reference product" is not acceptable as the sponsor has not provided evidence that the observed differences in the shape of the plasma concentration-time profiles after administration of the proposed (Test) product with food will not affect the safety or efficacy of the product. The proposed (Test) ER formulation may be labeled to be taken in the fasting state only. Considering that the RLD does not have this limitation, this may lead to dosing errors and confusion, which may have safety repercussions.

2) The 1500 mg Test ER formulation showed dose dumping potential at the highest alcohol concentration ((b) (4) %) in the in vitro studies. There is no alcohol dumping observed for RLD and the labeling of the RLD does not have a statement to limit the alcohol use. The Division has concern that adding alcohol use limitation for the proposed ER formulation may lead to safety repercussions. This issue could potentially be resolved, if the sponsor conducts an *in vivo* study to evaluate the impact of the observed *in vitro* effect.

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The clinical pharmacology and biopharmaceutics findings are as follows:

- No new clinical pharmacology information is available for Levetiracetam ER Tablets, nor was any new information identified in a search of the published literature. The sponsor plans to include the same information in their labeling as is provided in the currently approved Keppra XR® label with the exception of the modifications to Absorption and Distribution Section by adding their BE results.
- Levetiracetam ER Tablets, 1500 mg were bioequivalent to Keppra XR® tablets, 2 x 750 mg in the fasted state.
- The first fed BE study (PKD_10_131, n=18), failed to meet BE criteria for C_{max}. The BE criteria for AUC were met.
- The sponsor repeated the study under fed conditions (Study PKD_10_272) in a larger population (n=22) omitting earlier sampling time points and adding additional time points at the later part of the plasma concentration profile; the proposed product was found to be BE to RLD.
- While study 272 showed BE under fed state, since study 131 of similar design and sample size did not demonstrate bioequivalence, further evaluation was conducted to look for what might be the reason for these differences. The study conditions and analytical method used were similar in both studies. While sampling times were different, there was no clear attributable reason for these different results.
- In addition, both fed pivotal studies (PKD_10_131 and PKD_10_272) showed widely disparate plasma concentration-time profiles for the Test formulation. About one third of the subjects in the fed pivotal studies and in a third developmental study (PKD_09_503) demonstrated a "prolonged pattern of release" following administration of the Test Extended Release Tablets. No reason could be identified for why some subjects had this profile after the Test but not after the Reference formulation when administered with food. A higher proportion of subjects had this "prolonged pattern" in Study PKD_10_131 than in PKD_10_272, resulting in lower mean C_{max} reported for this study.
- The proposed product showed dose dumping potential at the highest alcohol concentration ((b) (4) %) in the in vitro studies while the labeling of the RLD does not have a statement for this potential.

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 Drug/Drug Product Information:

Dosage Form: The proposed product is a "Wrap Matrix" dosage form consisting of: Bilayer tablet (Drug layer and Openable layer), Functional coat and Top coat. Laser drilling is done on color layer side only.

Wrap Matrix: Dosage form Design

Strengths: 1000 mg and 1500 mg

Indication: adjunctive therapy in the treatment of partial onset seizures in patients ≥ (b) (4) years of age with epilepsy

Pharmacologic Class: antiepileptic drugs (AEDs)

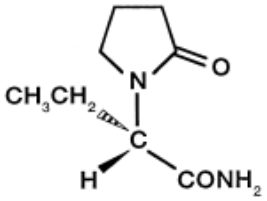
Chemical Name: (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide

Company or laboratory code(s): SPARCL

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.

Formulation:

Components	Amount (mg)/Tablet		Amount % w/w
Strength	1000 mg	1500 mg	1000 mg and 1500 mg
[redacted]			(b) (4)
Levetiracetam, USP	1000.00	1500.00	(b) (4)
Povidone (b) (4) USP			(b) (4)
Hypromellose (b) (4) USP (b) (4) (b) (4)			
Amino Methacrylate Copolymer, NF (b) (4) (b) (4)			
Colloidal silicon dioxide, NF			
Magnesium stearate, NF (b) (4)			
Talc, USP (b) (4)			

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:

Same dosing and route of administration as described in the most current labeling for Keppra XR®: 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?

Three single-dose, randomized, open-label, crossover bioequivalence (BE) studies were conducted to compare the final proposed formulation of Levetiracetam ER Tablets, 1500 mg to the RLD, Keppra XR® Tablets (2 x 750 mg) in healthy adult subjects under fasted and fed conditions. The sponsor also conducted fasted and fed BE studies with four

earlier pilot formulations of Levetiracetam ER Tablets, 1500 mg. A waiver of the need for an in vivo study of the lower strength is included, supported by the composition proportionality of the tablets and the results of multi-media *in vitro* dissolution testing. *In vitro* dissolution in alcoholic media has also been studied.

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

Not applicable (NA), bioequivalence studies only 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 ER formulation adequately supported by the clinical trials?

No. Levetiracetam ER Tablets, 1500 mg were bioequivalent to Keppra XR® tablets, 2 x 750 mg in the fasted state. The first fed BE study (n=18), failed to meet BE criteria for Cmax, the BE criteria for AUC were met. The sponsor repeated the study under fed conditions in a larger population (n=22) and omitting earlier sampling time points and adding additional time points at the later part of the plasma concentration profile; the proposed product was found to be BE to RLD.

SUMMARY OF STATISTICAL ANALYSIS LEVETIRACETAM

Fasted Study PKD_10_130 (n=18)

Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV%	P-value [4]
	Test	Reference	Test	Reference				
AUC_{0-t}	5.96	5.98	388.00	396.97	97.74	83.40 to 114.54	27.77	0.8045
AUC_{0-inf}	5.98	6.01	396.24	405.68	97.67	83.27 to 114.56	27.93	0.7999
C_{max}	3.10	3.15	22.25	23.22	95.84	81.80 to 112.27	27.71	0.6453

[4]P-value is for product effect

Fed Study PKD_10_131 (n=18)

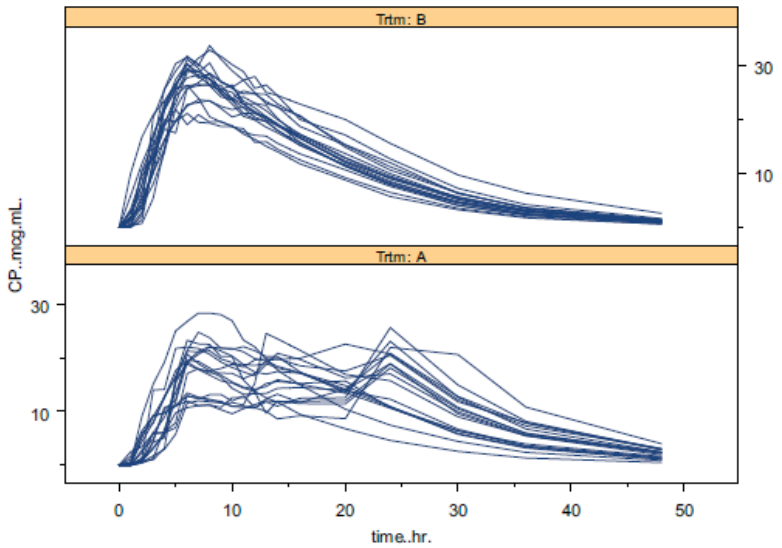
Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV%	P-value [4]
	Test	Reference	Test	Reference				
AUC_{0-t}	6.18	6.22	484.86	501.74	96.64	92.74 to 100.69	7.07	0.1655
AUC_{0-inf}	6.23	6.24	507.96	515.02	98.63	94.28 to 103.17	7.75	0.6001
C_{max}	3.09	3.33	21.93	27.88	78.67	75.96 to 81.47	6.03	<0.0001

Fed Study PKD_10_272 (n=22)

Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV%	P-value [4]
	Test	Reference	Test	Reference				
AUC_{0-t}	6.16	6.14	475.30	466.37	101.92	95.05 to 109.27	13.41	0.6439
AUC_{0-inf}	6.20	6.17	491.76	478.40	102.79	95.87 to 110.22	13.41	0.5035
C_{max}	3.22	3.26	25.03	26.00	96.27	87.65 to 105.75	18.12	0.4931

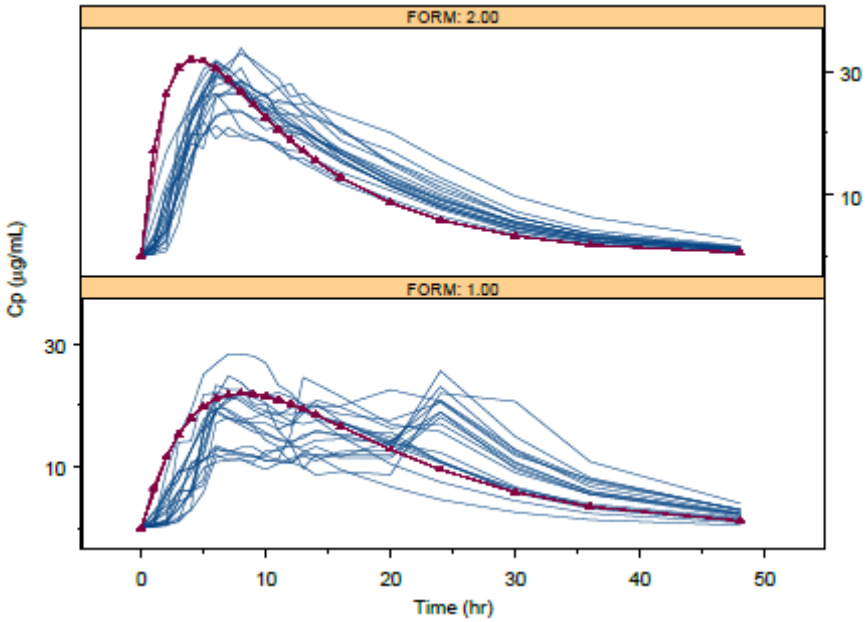
However, both fed pivotal studies (PKD_10_131 and PKD_10_272) showed widely disparate plasma concentration-time profiles for the Test formulation. About one third of the subjects in the fed pivotal studies and in a third developmental study (PKD_09_503) demonstrated a "prolonged pattern of release" following administration of the Test Extended Release Tablets. No reason could be identified for why some subjects had this profile after the Test but not after the Reference formulation when administered with food. A higher proportion of subjects had this "prolonged pattern" in Study PKD_10_131 (N=10) than in PKD_10_272 (N=6), resulting in lower mean C_{max} reported for this study.

Levetiracetam plasma concentration-time profiles in the fed pivotal study PKD_10_131 (Trtm A: Test formulation, Trtm B: Reference formulation)



The sponsor conduced simulations suggesting that the Test and the Reference product are likely to be bioequivalent at steady state (based on AUC and Cmax). However, the steady state simulations conducted by the sponsor are not acceptable for Study PKD-10-131 (which failed to pass BE criteria for Cmax after single dose), since the pharmacokinetic model does not describe the time course of drug concentrations adequately.

Observed (blue) and mean predicted (red) plasma concentration of test and reference formulations of study PKD 10 131 (Form 1=Test, Form 2=Reference)

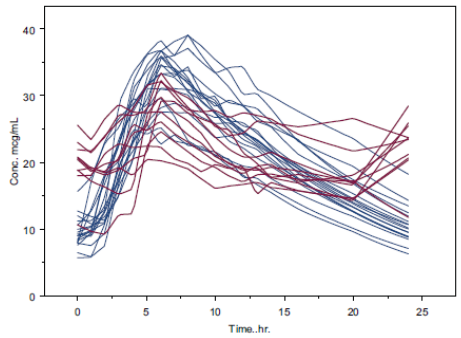


The sponsor provided additional repeated dose simulation by superposition method. Observed plasma concentrations of subjects in the Test product arm who showed "prolonged pattern of release" from study PKD-10-131 were used and superposition method was followed to simulate steady state plasma concentration over 24-hour dosing intervals on Days 2, 3, 4, and 5 using WinNonlin v.5.3. Similarly, Reference arm data from Study PKD-10-131 and PKD-10-130 were used to simulate steady state concentrations. Steady state data of Test (with prolonged pattern of release) was compared with Reference arm steady state data in both the fasted and fed conditions. The results of the simulation show that in subjects with "prolonged pattern of release" on Day 2-Day 5:

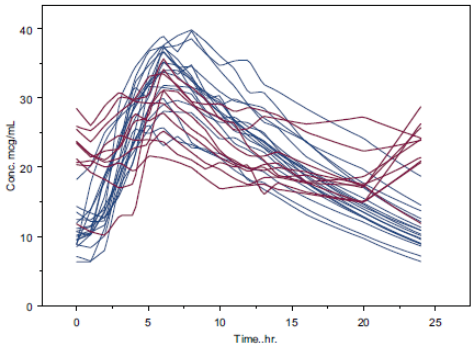
- Trough concentrations (mean and minimum) were higher than the corresponding values for the reference treatment under both the fed and fasted conditions.
- AUC_{0-24} (mean values) after repeated dosing were generally similar for all treatments.
- C_{max} (mean values) for subjects with "prolonged pattern of release" were lower than the reference treatment only under the fed condition but were within the range observed for individual concentrations for reference dosed under fed conditions.

Day 2-Day 5 Plasma Levetiracetam concentration profiles for Reference (all subjects) and Test subjects with prolonged profiles (Study PKD-10-131) are provided below, (Reference- blue line, Test- red line):

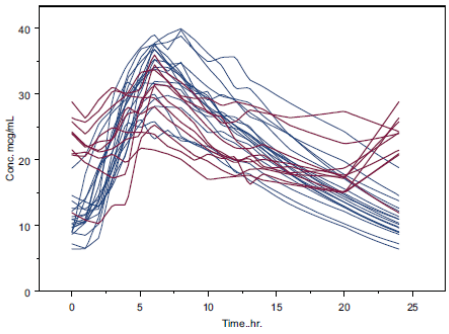
Day 2



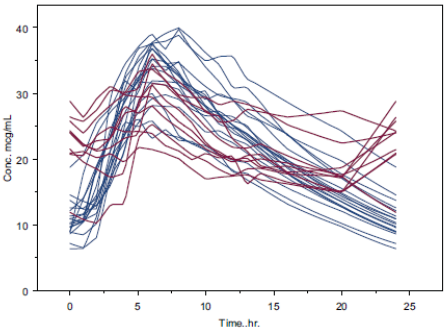
Day 3



Day 4



Day 5



The sponsor's simulations did not demonstrate that the individual plasma concentration-time profiles after administration of the Test formulation at steady state will be similar in shape to that of the Reference formulation.
Additionally, the sponsor claims that "the range of trough concentrations resulting in subjects with prolonged pattern of release fall within the range of observed trough concentrations of 4.6-21 μg/mL in responders at 12-hour with Keppra" based on Clinical Pharmacology and Biopharmaceutics Review (Levetiracetam KEPPRA XR).
This claim is not acceptable since the relationship between levetiracetam PK and PD profiles is not sufficiently well understood to justify approval based on trough levels. In addition, another sponsor's FDA review can not be referenced in a 505(b)(2) application.

Therefore, the sponsor's claim that "there is no safety and / or efficacy risk and the SPARCL formulation is predicted to behave similar to reference product " is not acceptable as the sponsor has not provided evidence that the observed differences in the shape of the plasma concentration-time profiles after administration of the proposed (Test) product with food will not affect the safety or efficacy of the product.
The Division is concerned that these differences may require that the NDA formulation be labeled to be taken only in the fasting state. However, the RLD does not have this limitation. Therefore, these labeling differences may lead to significant errors in administration, which may have safety repercussions.

2.2.6 Does Levetiracetam prolong QT or QTc interval?

No new QT information is available for Levetiracetam ER Tablets, nor was any new information identified in a search of the published literature.

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

Yes. A Pre-Approval Data Validation Inspection, conducted by the Office of Scientific Investigations (January 15, 2013), found the method validation and the actual assay of the subject plasma samples to be acceptable.
Methodology: LC/MS-MS
Extraction Method: Solid Phase Extraction (SPE)
Analytes Assayed: Levetiracetam
Internal Standard: (b) (4)
Matrix: Human Plasma
Anticoagulant: K_2EDTA
Analytical Site (for all studies): (b) (4)
(b) (4)

2.2.8 What are the general ADME characterstics of Levetiracetam ER?

No new clinical pharmacology information is available for Levetiracetam ER Tablets. The sponsor plans to include the same information in their labeling as is provided in the currently approved Keppra XR® label with the exception of the modifications to Absorption and Distribution Section by adding their BE results.

Modifications to Absorption and Distribution Section proposed by the sponsor:

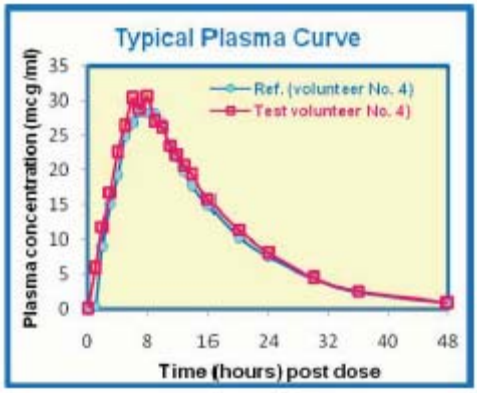
- Levetiracetam extended-release tablets 1500 mg are bioequivalent to Keppra XR* (2 × 750 mg) tablets respectively, in both fasted and fed states.

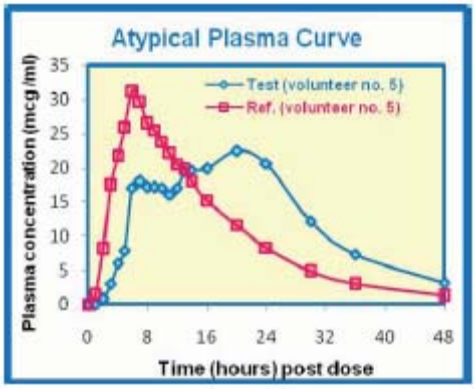
For the other ADME information, please refer to the current approved Keppra XR® label.

2.2.9 What are the basic pharmacokinetic parameters of Levetiracetam ER after single and multiple doses?

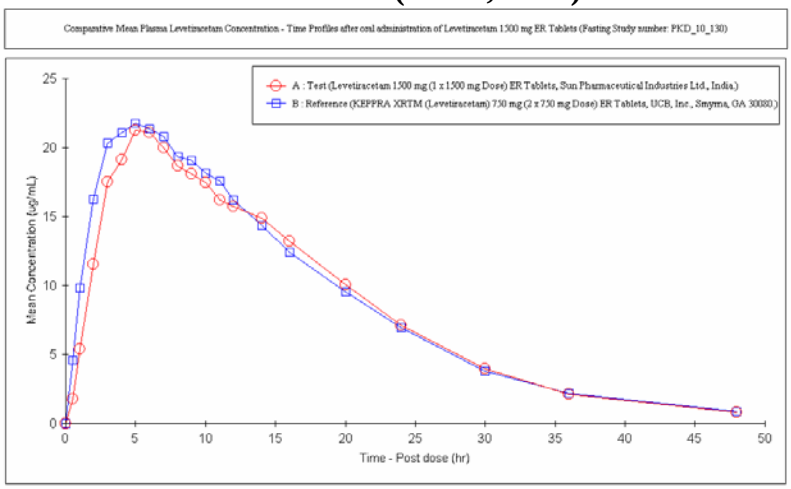
Levetiracetam ER Tablets had similar PK profile to that of Keppra XR in the fasted state. However, both fed pivotal studies (PKD_10_131 and PKD_10_272) showed widely disparate individual plasma concentration-time profiles for the Test formulation. About one third of the subjects in the fed pivotal studies demonstrated a "prolonged pattern of release" following administration of the Test Extended Release Tablets. No reason could be identified for why some subjects had this profile after the Test but not after the Reference formulation when administered with food. A higher proportion of subjects had this "prolonged pattern" in Study PKD_10_131 than in PKD_10_272, resulting in lower mean C_{max} reported for this study.

No multiple dose studies were conducted with the proposed Levetiracetam ER formulation.

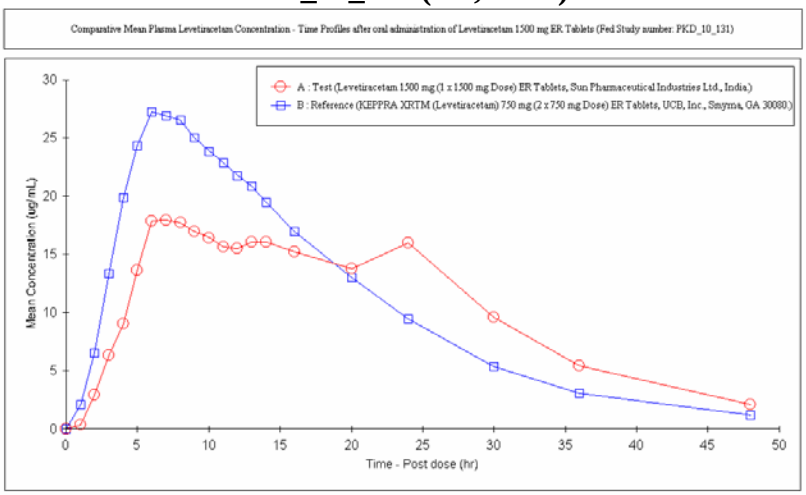




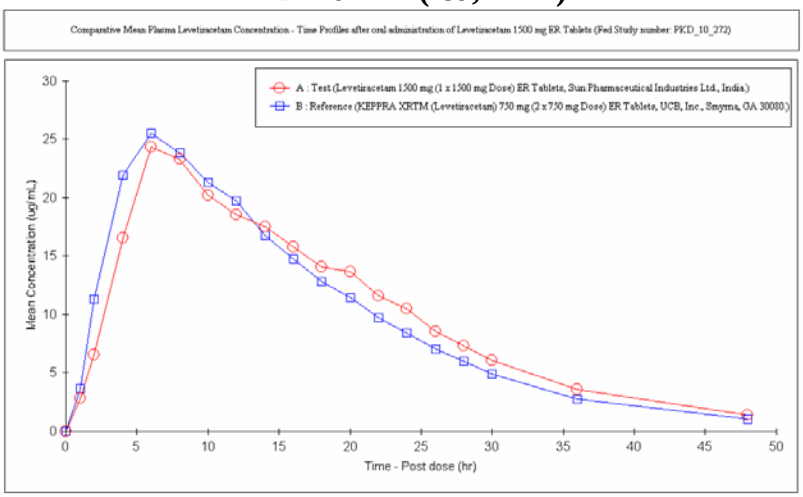
Mean plasma concentration profile of Levetiracetam after Levetiracetam 1500 mg ER Tablet/Keppra XR® (Levetiracetam) 750 mg (2 x 750 mg Dose) ER Tablet PKD 10 130 (fasted, n=18)



Mean plasma concentration profile of Levetiracetam after Levetiracetam 1500 mg ER Tablet/Keppra XR® (Levetiracetam) 750 mg (2 x 750 mg Dose) ER Tablet PKD_10_131 (fed, n=18)



Mean plasma concentration profile of Levetiracetam after Levetiracetam 1500 mg ER Tablet/Keppra XR® (Levetiracetam) 750 mg (2 x 750 mg Dose) ER Tablet PKD 10 272 (fed, n=22)



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

NA

2.2.11 What is the variability in the PK data?

Keppra XR has low intra- and inter-subject PK variability (label). Levetiracetam ER Tablets had similar PK profile and variability to that of Keppra XR in the fasted state, however the variability in C_{max} and T_{max} in the fed state was much higher for Levetiracetam ER Tablets compared to RLD (Keppra XR), see table below.

Parameters	Levetiracetam 1500 mg ER Tablet Test (A)				KEPPRA XR™ (Levetiracetam) 750mg (2 x 750mg Dose) ER Tablet Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-t} (µg.h/mL)	481.1357	±	91.43065	19.0	469.9453	±	60.43293	12.9
AUC_{0-inf} (µg.h/mL)	497.9899	±	95.55574	19.2	482.4197	±	64.88473	13.4
C_{max} (µg/mL)	25.9068	±	7.19525	27.8	26.0669	±	2.83015	10.9
T_{max} (h)	8.364	±	4.2150	50.4	6.182	±	1.0527	17.0
T_{max}* (h)	8.00 (4.00 – 20.00)	±	-	-	6.00 (4.00 – 8.00)	±	-	-
K_{el} (h^{-1})	0.08530	±	0.009510	11.1	0.08781	±	0.009246	10.5

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

NA.

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

NA.

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?

No new clinical pharmacology information is available for Levetiracetam ER Tablets, nor was any new information identified in a search of the published literature. All of the RLD information with respect to special populations is also applicable to Levetiracetam 1000 mg and 1500 mg ER Tablets, with the exception of use in patients with renal impairment. Levetiracetam clearance is correlated with creatinine clearance and therefore lower doses (500 to 1500 mg) are recommended in patients with moderate or severe impaired renal impairment. Since these doses cannot be achieved with the available ER tablet strengths, the sponsor proposes to modify Section 2.1 the label to "not recommended in patients with moderate or severe impaired renal impairment".

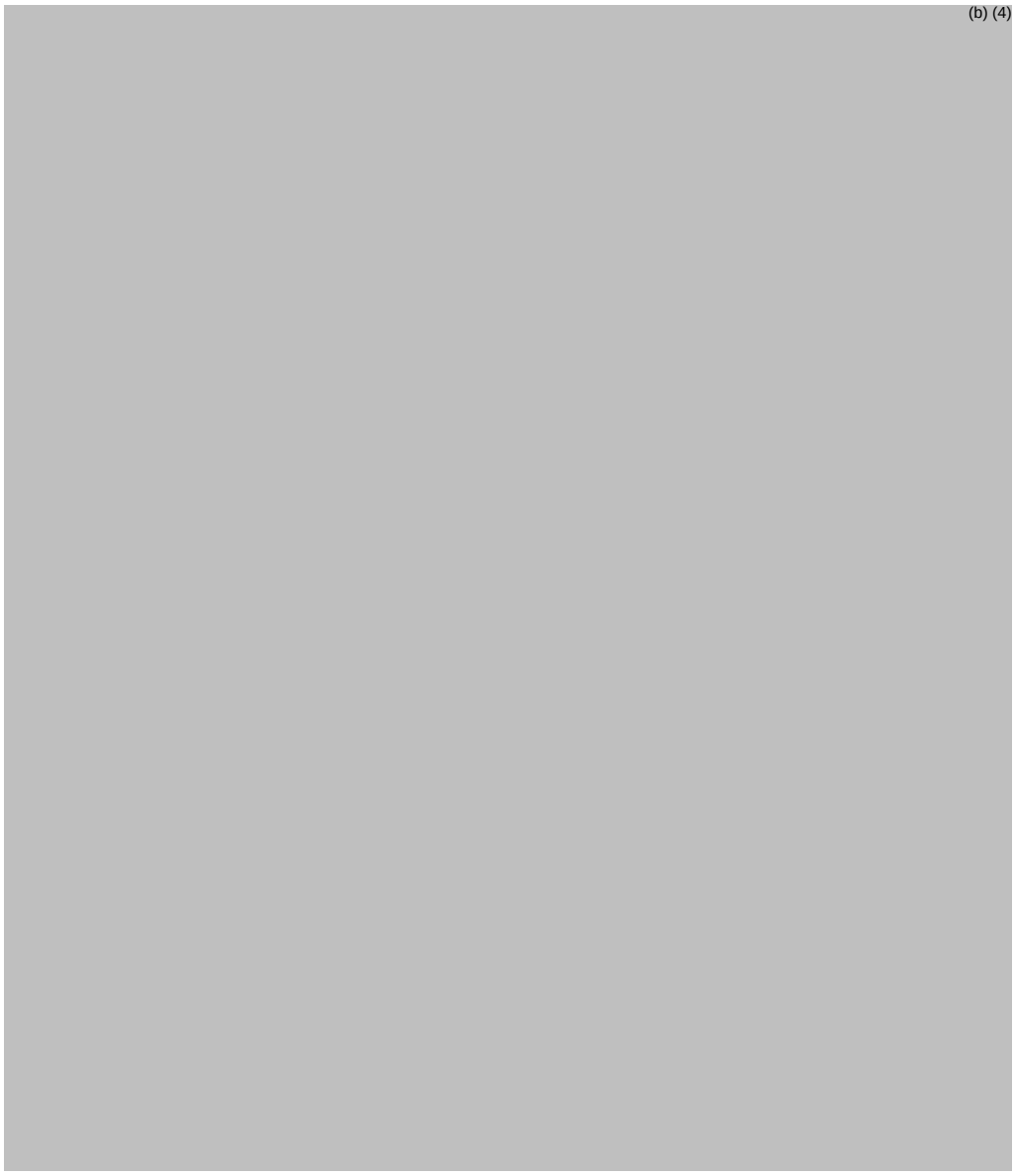
2.4 EXTRINSIC FACTORS

No new clinical pharmacology information regarding extrinsic factors is available for Levetiracetam ER Tablets.

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 XR label). The *in vitro* alcohol dose dumping study results for Levetiracetam ER are summarized below: At the lower alcohol concentrations (b) (4), the dissolution profiles were similar to those without alcohol, however at the highest alcohol concentration (b) (4)%), the dissolution profiles showed difference as shown in the following figures for the 1000 mg and 1500 mg strengths, respectively. The dissolution method used was USP III 230 mL 0.1 N HCl with 15 dpm.



In ANDA 203059, which included the 500 and 750 mg strengths by the same sponsor, the in vitro alcohol dose dumping study (b) (4) did not show dose dumping potential.
The reference Keppra XR (NDA 22-285) did not show dose dumping potential with alcohol.

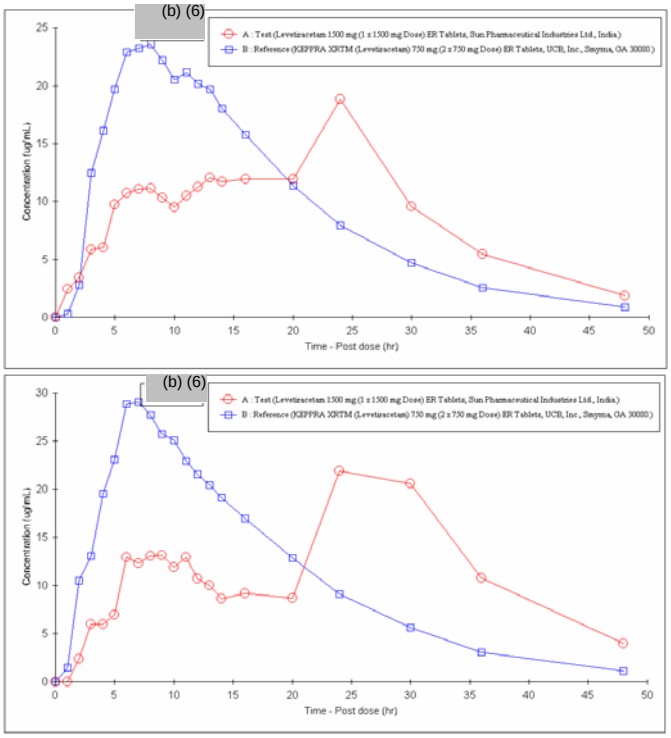
2.5.2 Is the proposed to-be-marketed formulation of Levetiracetam ER bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

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?

The effect of food on the bioavailability of levetiracetam from the proposed product appears to be unpredictable. Both fed pivotal studies (PKD_10_131 and PKD_10_272) showed widely disparate plasma concentration-time profiles for the Test formulation. About one third (28%) of the subjects in the fed pivotal studies and in a third developmental study (PKD_09_503) demonstrated a "prolonged pattern of release" following administration of the Test Extended Release Tablets. The sponsor believes that this may be a result of varying gastric emptying time for the dosage form as well as movement throughout the gastrointestinal tract.
A higher proportion of subjects had this "prolonged pattern" in Study PKD_10_131 than in PKD_10_272, resulting in lower mean C_{max} reported for this study. No reason could be identified for why some subjects had this profile after the Test but not after the Reference formulation when administered with food and for the higher % of subjects with this profile in study PKD_10_131. Both fed studies were carried out at the same location in the same facilities (SPARCL's Phase 1 Unit in Baroda, India) and under the direction of the same investigator. The batch numbers of the Test product (SPARCL's Levetiracetam Extended Release Tablets; JKJ1197B) and reference product (Keppra® XR; 52943) used in each study were the same. The meals administered in Studies PKD_10_131 and PKD_10_272 are very similar. Analysis of the samples was done using similar analytical methods.

Examples of Individual plasma concentration profiles of Levetiracetam after Levetiracetam 1500 mg ER Tablet/Keppra XR® (Levetiracetam) 750 mg (2 x 750 mg Dose) ER Tablet administered under fed condition



2.6 ANALYTICAL

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

Levetiracetam concentrations in human plasma were quantified using a validated high performance liquid chromatographic /Tandem Mass Spectrometry method. Levetiracetam was extracted from plasma using Solid Phase Extraction.
The validation results from Levetiracetam bioanalytical assay are are considered acceptable and the results are presented in the table below.

Validation Parameters for Levetiracetam Bioanalytical Assay

Analyte	Levetiracetam		
Internal Standard (IS)	(b) (4)		
Limit of quantitation	LLOQ : 0.220µg/mL, ULOQ : 39.984µg/mL LLOQ : 0.221µg/mL, ULOQ : 39.959µg/mL(*) LLOQ : 0.224µg/mL, ULOQ : 39.840µg/mL (*)		
Average recovery of analyte (%)	QC Low A: 96.1%, QC Low B: 96.0% QC Med A: 89.3%, QC Med B: 93.8%, QC High : 93.5%		
Average recovery of IS (%)	84.7%		
Standard curve concentrations (µg/mL)	0.220, 0.440, 2.259, 7.497, 9.996, 18.992, 27.489, 32.487, 39.984 0.221, 0.441, 2.266, 7.521, 10.027, 19.052, 27.576, 32.589, 39.959(*) 0.224, 0.448, 2.241, 7.470, 9.960, 18.924, 27.390, 32.370, 39.840(*)		
QC Concentrations (µg/mL)	QC Low-A :0.659 QC Low-B :1.976 QC Med-A :8.982 QC Med-B :19.661 QC High :33.683	QC Low-A: 0.661(*) QC Low-B: 1.982(*) QC Med-A: 9.010(*) QC Med-B: 19.723(*) QC High: 33.789(*)	QC Low-A: 0.668(*) QC Low-B: 2.004(*) QC Med-A: 8.973(*) QC Med-B: 19.641(*) QC High: 33.648(*)
QC Intraday precision range (%)	1.7% to 6.9%		
QC Intraday accuracy range (%)	93.4% to 103.4%		
QC Inter day precision range (%)	Including failed P&A: 0.7% to 34.1%, 1.1% to 3.5%, 1.0% to 7.1%		
	Excluding failed P&A: 0.7% to 9.5%, 1.1% to 3.5%, 1.0% to 7.1%		
QC Inter day accuracy range (%)	Including failed P&A: 84.0% to 118.7%, 89.9% to 99.2%, 102.1% to 111.7%		
	Excluding failed P&A: 88.1% to 109.5%, 89.9% to 99.2%, 102.1% to 111.7%		
Bench-top stability (hrs)	7 hours at room temperature		
Stock solution stability (days)	16 days @ 2-8°C		
Post-Processed stability (hrs)	56 hours @ 10°C ± 2°C		
Post Extraction Bench Top Stability	18 hours at room temperature		
Freeze-thaw stability (cycles)	03 cycles		
Long term storage stability (Days)	26 days @ (-20°C ± 5°C), 56 days @ (-35°C ± 5° C, -65°C± 10° C)		
Dilution Integrity	3 – 4 times of ULOQ Concentration (124.750µg/mL) diluted 10 folds.		
	% Accuracy : 1/10th : 92.6		
	% Precision : 1/10th : 5.7		
Selectivity	No interference observed in blank plasma samples		

(*): The calibration standards and Quality control samples were prepared for Long term storage stability experiment.

3.0 DETAILED LABELING RECOMMENDATION

No labeling recommendations will be sent to the sponsor in this review cycle.

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/s/

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