CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202543Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW

Office of New Drug Quality Assessment

Application No.:	NDA 202-543	**Reviewer:** Angelica Dorantes, Ph.D	
Submission Date:	January 13, 2011	**Supervisor:** Patrick J. Marroum, Ph.D	
Division:	DNP	**Date Assigned:**	February 2, 2011
Sponsor:	HQ Specialty Pharma Corporation	**Date of Review:**	August 26, 2011
Trade Name:	Levetiracetam Injection, (b) (4) (b) (4)	**Type of Submission:** 505 (b)(2) NDA	
Generic Name:	Levetiracetam Injection		
Indication:	Levetiracetam Injection, (b) (4) is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults with idiopathic generalized epilepsy.		
Formulation/ strengths	Injectable Solution/ One bag of Levetiracetam Injection, (b) (4) contains; 500 mg/100 mL (5 mg/mL), or 1000 mg/100mL (10 mg/mL), or 1500 mg/100mL (15 mg/mL) Levetiracetam Injection, (b) (4) should not be further diluted prior to its use.		
Route of Administration	Intravenous use only		
Type of Review:	***Biowaiver Request***		

SUBMISSION:

HQ Specialty Pharma Corporation submitted NDA 202-543 for Levetiracetam Injection, (b) (4) (b) (4) (5 mg/ml, 10 mg/ml, and 15 mg/ml) under 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act. This product has the same dosage form, active and inactive ingredients, route of administration, and indications as the Reference Listed Drug, KEPPRA® Injection 5 ml/vial (100 mg/ml) by UCB. Currently, Levetiracetam Injection is approved in the United States under NDA 21-872 (approval date, July 31, 2006) only as a concentrated solution, 100 mg/mL packaged in 5 mL vials, which requires dilution to 5 mg/mL in infusion fluids [sodium chloride (0.9%) injection, USP, lactated ringer's injection or dextrose 5% injection] prior to administration. It is marketed in the United States under the brand name KEPPRA® by UCB Inc. since 2006.

BIOPHARMACEUTICS INFORMATION:

Formulation: The compositions of the proposed formulations for the Levetiracetam Injection, (b) (4) 500 mg/100 mL (5 mg/mL), 1000 mg/100mL (10 mg/mL) and 1500 mg/100mL (15 mg/mL) are described below.

Compositions of Levetiracetam Injection, (b) (4) 500mg/100 mL (5mg/ml, 1000mg/100 mL (10 mg/ml), and 1500mg/100 mL (15 mg/mL)

Name of Ingredients	Composition		Composition		Composition	
	mg /mL	mg per 100 mL container	mg /mL	mg per 100 mL container	mg /mL	mg per 100 mL container
Levetiracetam *	5.0	500	10	1000	15	1500
Sodium Chloride	8.2	820	7.5	750	5.4	540
Glacial Acetic Acid	0.055	5.5	0.065	6.5	.075	7.5
Sodium Acetate Trihydrate	1.64	164	1.64	164	1.64	164
(b) (4) Glacial Acetic Acid	(b) (4)					
WFI						
Total	**1 mL**	**100 mL**	**1 mL**	**100 mL**	**1 mL**	**100 mL**
Theoretical Number of Containers	**NA**	**1**	**NA**	**1**	**NA**	**1**

It should be noted that Keppra Injection is a concentrated solution that requires dilution to a final concentration of 5 mg/mL prior to intravenous infusion. The proposed Levetiracetam Injection, (b) (4) is prepared as a ready-to-infuse solution.

The active ingredient, Levetiracetam is described as a white crystalline powder that is very soluble in water and freely soluble in chloroform, methanol and ethanol. The maximum daily dose for Levetiracetam Injection, (b) (4), is 3000 mg/day.

BIOWAIVER REQUEST:

In this submission, the Applicant is requesting a waiver from the CFR's requirement to provide data from an in vivo bioequivalence study comparing the proposed Levetiracetam Injection, (b) (4) (5mg/ml) to the RLD product, KEPPRA® Injection 5 ml/vial (100 mg/ml) by UCB. The following table presents a comparison of the proposed drug product and the reference listed drug.

Comparison of Compositions of Levetiracetam Injection, (b) (4) and Reference Listed Drug (RLD) Keppra® Injection

Levetiracetam Injection, (b) (4) 500 mg/100 mL (5 mg/mL)	**Levetiracetam Injection, (b) (4) (b) (4) 1000 mg/100 mL (10 mg/mL)**	**Levetiracetam Injection, (b) (4) (b) (4) 1500 mg/100 mL (15 mg/mL)**	**RLD: Keppra Injection 5 mL vial (100 mg/ mL)***
Approximately 0.8% Sodium Chloride	Approximately 0.75% Sodium Chloride	Approximately 0.5% Sodium Chloride	0.45% Sodium Chloride[1]
Sodium Acetate Trihydrate	Sodium Acetate Trihydrate	Sodium Acetate Trihydrate	Sodium Acetate Trihydrate
Glacial Acetic Acid	Glacial Acetic Acid	Glacial Acetic Acid	Glacial Acetic Acid
WFI	WFI	WFI	Water

*Requires reconstitution.
[1] when reconstituted with sodium chloride (saline), the final product infused is approximately 0.9%

Comparison of Levetiracetam Injection, (b) (4) and RLD, Keppra Injection: The following table presents the information comparing the conditions of use, active ingredient, route of administration, dosage form and strength [at the time of administration] of the proposed

drug product are the same as those of the reference listed drug.

Product:	Proposed Drug Product	Reference Listed Drug
Product Proprietary Name:	None	Keppra®
Product Established name	Levetiracetam Injection, (b) (4) (b) (4) 500 mg/100 mL (5 mg/mL), 1000 mg/100 mL (10 mg/mL) and 1500 mg/100 mL (15 mg/mL)	Levetiracetam Injection, solution, concentrate
Conditions of Use:	Partial Onset Seizures, Myoclonic Seizures in Patients with Juvenile myoclonic Epilepsy, Primary Generalized Tonic-Clonic Seizures	Partial Onset Seizures, Myoclonic Seizures in Patients with Juvenile myoclonic Epilepsy, Primary Generalized Tonic-Clonic Seizures
Active Ingredient(s):	Levetiracetam, USP	Levetiracetam
Inactive Ingredients:	Sodium acetate trihydrate Sodium chloride Glacial acetic acid WFI (Water for Injection)	Sodium acetate trihydrate Sodium chloride Glacial acetic acid Water
Route of Administration:	Injectable	Injectable
Dosage Form:	IV (Infusion)	IV (Infusion)
Strength:	500 mg/100 mL (5 mg/mL), 1000 mg/100 mL (10 mg/mL) and1 500 mg/100 mL (15 mg/mL)	500 mg/5 mL
Package Size	100 mL dual port flexible (b) (4) (b) (4) IV bags, containing 500 mg [5 mg/mL], 1000 mg [10 mg/mL] or 1500 mg [15 mg/mL] levetiracetam, ready for administration	5 mL glass vials containing concentrated solution of 500 mg levetiracetam. The solution is diluted to 5 mg/mL prior to administration

RECOMMENDATION:

The Office of New Drug Quality Assessment (ONDQA)-Biopharmaceutics has reviewed the information included in NDA 202-543 for Levetiracetam Injection (b) (4) Based on the evaluation of the provided information, Biopharmaceutics considers that the Applicant's request for a waiver of the CFR's requirement to provide in vivo BE data to support the approval of their product is acceptable and the biowaiver for the proposed Levetiracetam Injection (b) (4) (b) (4) (5 mg/mL, 10 mg/mL, and 15 mg/mL) is granted.

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/s/

ANGELICA DORANTES
08/29/2011

BIOPHARMACEUTICS

Office of New Drugs Quality Assessment

Application No.:	NDA 202-543	**Reviewer:** Angelica Dorantes, Ph.D	
Submission Date:	January 13, 2011	**Supervisor:** Patrick J. Marroum, Ph.D	
Division:	DNP	**Date Assigned:**	February 2, 2011
Sponsor:	HQ Specialty Pharma Corporation	**Date of Review:**	March 2, 2011
Trade Name:	Levetiracetam Injection, (b) (4) (b) (4)	**Type of Submission:** 505 (b)(2) NDA	
Generic Name:	Levetiracetam Injection		
Indication:	Levetiracetam Injection, (b) (4) is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults with idiopathic generalized epilepsy.		
Formulation/ strengths	Injectable Solution/ One bag of Levetiracetam Injection, (b) (4) contains 500 mg levetiracetam (500 mg/100 mL; 5 mg/mL) Levetiracetam Injection, (b) (4) should not be further diluted prior to its use.		
Route of Administration	Intravenous use only		
Type of Review:	***Filing Review – Biowaiver Request***		

SUBMISSION:

HQ Specialty Pharma Corporation submitted NDA 202-543 for Levetiracetam Injection, (b) (4) (b) (4) n 5 mg/ml under 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act. This product has the same dosage form, active and inactive ingredients, route of administration, and indications as the Reference Listed Drug, KEPPRA® Injection 5 ml/vial (100 mg/ml) by UCB. Currently, Levetiracetam Injection is approved in the United States under NDA 21-872 (approval date, July 31, 2006) only as a concentrated solution, 100 mg/mL packaged in 5 mL vials, which requires dilution to 5 mg/mL in infusion fluids [sodium chloride (0.9%) injection, USP, lactated ringer's injection or dextrose 5% injection] prior to administration. It is marketed in the United States under the brand name KEPPRA®3 by UCB Inc. since 2006.

RECOMMENDATION:

The Biopharmaceutics review for this NDA submission will be focused on the evaluation and acceptability of the information supporting the applicant's request for a waiver of the CFR's requirement to provide in vivo bioavailability/bioequivalence to support the approval of their proposed product. From the ONDQA-Biopharmaceutics perspective, NDA 202-543 for Levetiracetam Injection, Ready-to-Infuse solution 5 mg/ml is fileable.

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03/14/2011

PATRICK J MARROUM
03/16/2011