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*APPLICATION NUMBER:*

**202543Orig1s000**

**MEDICAL REVIEW(S)**

## Clinical Review

Application Type	NDA
Application Number	202543
Priority or Standard	Standard
Submit Date	1/13/11
Received Date	1/13/11
PDUFA Goal Date	11/13/11
Division/Office	DNP
Reviewer Name	Martin S. Rusinowitz, MD
Review Completion Date	10/9/11
Requested Established Name	 (b) (4)
Approved Established Name	levetiracetam in sodium chloride injection
(Proposed) Trade Name	None
Therapeutic Class	Anticonvulsant
Applicant	HQ Specialty Pharma Corp.
Formulation(s)	Levetiracetam in 0.82% NaCl injection (500mg/100 mL) Levetiracetam in 0.75% NaCl injection (1000mg/100 mL) Levetiracetam in 0.54% NaCl injection (1500mg/ 100
Dosing Regimen	Intravenously over 15 minutes
Indication	Partial Onset, Myoclonic and Primary Generalized Tonic-Clonic Seizures
Intended Population	Adults 16 Years and Older

## 1. Introduction

Keppra Injection for intravenous use is currently approved under NDA 021872 (approval date 7/13/06) as a concentrated solution of levetiracetam 100 mg/mL in a 5 mL vial that requires a 20-fold dilution to 5 mg/mL in infusion fluids (sodium chloride 0.9% injection, lactated ringers or dextrose 5% injection) prior to administration. It has been marketed as such by UCB, Inc. since 2006. When mixed with the above recommended diluents it is stable for at least 24 hours when stored in polyvinyl chloride bags at room temperature.

HQ Specialty Pharma Corporation is submitting a 505(b)(2) New Drug Application for levetiracetam in sodium chloride injection, 500 mg/100 mL (5 mg/mL), 1000 mg/100 mL (10 mg/mL) and 1500 mg/100 mL (15 mg/mL). This is a premixed levetiracetam formulation that will not require additional mixing and dilution, and can be directly infused as provided. The filing is based upon the reference listed drug (RLD) product Keppra Injection, 500 mg/5 mL described above. This application provides for a change in composition/dosage form, from a 5 mL vial containing 500 mg of Levetiracetam Injection (100 mg/mL) requiring reconstitution prior to administration to a ready-to-infuse solution (5 to 15 mg/mL) packaged in a 100 mL flexible (b) (4) dual port bags containing 500, 1000 or 1500 mg of levetiracetam.

Levetiracetam injection, (b) (4) has the same indications as the RLD; it is indicated for partial onset seizures, myoclonic seizures in patients with juvenile myoclonic epilepsy and primary generalized tonic-clonic seizures.

Financial disclosure information was not submitted by the Sponsor, as there were no clinical studies submitted as part of this NDA.

## 2. Background

Keppra has been approved as adjunctive therapy for oral use in the management of partial onset, myoclonic, and primary generalized tonic-clonic seizures in adults and pediatric patients 4 years of age and older since 1999. Keppra Injection for intravenous use has been available since 2006. It is indicated in patients 16 years of age and older who are unable to take oral medication, but who need to maintain previously prescribed oral levetiracetam or for those who are beginning initial levetiracetam therapy.

HQ Pharma has provided the following table to outline a comparison of their drug product to the RLD.

Product:	Proposed Drug Product	Reference Listed Drug
Product Proprietary Name:	None	Keppra®
Product Established name	Levetiracetam Injection, (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) and 1500 mg/100 mL (15 mg/mL)	500 mg/5 mL
Package Size	100 mL dual port (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

HQ Specialty Pharma asserts the following key features of their proposed product:

- Same qualitative formulation as Keppra Injection
- Same indications as Keppra Injection
- Same directions for drug administration as Keppra Injection
- Proposed Levetiracetam Injection, (b) (4) is ready for administration and does not require further dilution as Keppra Injection.
- It is iso-osmotic having osmolarity between 275-345 mOsms. Osmolarity of the RLD solutions are between 359-420 mOsms.

- Proposed Levetiracetam Injection, (b) (4) eliminates any potential of microbial contamination during its preparation in the hospital pharmacy.
- It is expected to be physically compatible and chemically stable for at least 24 months, when packaged in (b) (4) bags and stored at controlled room temperature (b) (4).
- Proposed Levetiracetam Injection, (b) (4) 100 mL flexible (b) (4) bags contain a dual port system for introducing other medications.
- Proposed Levetiracetam Injection, (b) (4) eliminates a step in the preparation of the medication for administration; it also eliminates the potential for inadvertent administration of the 20-fold concentrated solution.
- It has potential to minimize waste as it does not have to be thrown out very next day if not used.

The following table, prepared by the Sponsor, provides a comparison between the RLD and their proposed ready-to-use product:

Parameter	UCB KEPPRA® Injection	HQ Levetiracetam Injection, (b) (4)	Comments
Brand Name	KEPPRA®	-	-
Active Ingredient	Levetiracetam	Levetiracetam	No Change
Container	5 mL USP Type 1 glass vials	100 mL flexible plastic (b) (4) containers	HQ Dual Port (b) (4) Infusion bags provide a package that is ready to use without further dilution required.
Formulation	Concentrate for dilution	Pre-mix, Ready-to-Use	HQ pre-mix formulation provides: <ul style="list-style-type: none"> <li>• Ready to use strength</li> <li>• A potentially safer alternative by eliminating medication administration errors related to inadvertent administration of concentrated solution</li> </ul>
Strength, (mg / mL)	100	5, 10 or 15	Concentration of HQ product is ready to use
Strength per Container (mg)	500	500, 1000 or 1500	No Change to recommendation based on patient response when compared to RLD Dosing Regimen
Manufacturing Process	(b) (4)		
Isotonicity	-	Isotonic	The measured Osmolarity of the RLD admix solutions ranged from 359-420 mOsm as compared to Osmolarity 275-345 mOsm
Storage	Premixed solution is stable for 24 hours in PVC bags, when stored at controlled room temperature	Premixed solution is stable for (b) (4) in (b) (4) bags, when stored at controlled room temperature	<ul style="list-style-type: none"> <li>• Potential for waste reduction that can occur due to changes in the patient orders, as the premixed solution may not be stable for more than 24 hours</li> <li>• Eliminates daily need for admixing of concentrate solution resulting in ready to use product, saving time and providing a safer alternative to use of concentrated solutions</li> </ul>
Directions for Administration	Infuse over 15 minutes	Infuse over 15 minutes	No change

Parameter	UCB KEPPRA® Injection	HQ Levetiracetam Injection, Ready-to-Infuse Solution	Comments
Directions for Preparation	Dilute with 100 mL infusion media to 5 mg/mL concentration before infusion	No preparation required	HQ product eliminates several steps and waste in the preparation of the solution: <ul style="list-style-type: none"> <li>• No need to withdraw concentrated solution from the vial</li> <li>• No need to secure a separate infusion bag</li> <li>• No need to transfer the solution from syringe to an infusion bag prior to administration</li> <li>• Dual port system provides added convenience for introducing other medications to the patients</li> <li>• Reduces hospital waste of empty syringes and needles</li> </ul>

### 3. CMC

Dr. Martha Heimann, CMC Lead, has reviewed this NDA and there do not appear to be any drug substance or drug product issues.

Dr Heimann did feel that certain terminology used in the label, carton, container and over-wraps were contrary to FDA policy. Thus, terminology such as (b) (4) should not appear in the label (b) (4)

For this reason the Sponsor was asked to strike this language. Unfortunately, the Sponsor has printed a large number of overwraps and containers. It was agreed in a teleconference that the Sponsor may use these materials, but must remove these statements on any subsequent printings.

### 4. Nonclinical Pharmacology/Toxicology

Levetiracetam possesses properties which suggest that not only does it suppress seizures but that it may also be antiepileptogenic. It has substantial efficacy in kindled and genetically epileptic animals. Although the exact mechanism of action of levetiracetam is not known, it appears to be unique, in that it has a specific binding site within the brain. It does not directly affect glutamate or GABA, does not alter Na<sup>+</sup> channel properties, produces a limited reduction in high-voltage-activated Ca<sup>2+</sup> currents (but not low-voltage) and possibly modulates intracellular Ca<sup>2+</sup> transients. It has little direct effect on GABA-

receptor mediated currents but opposes the action of negative modulators of GABA and glycine receptors. It may bind to the synaptic vesicle protein, SV2A.

At a pre-NDA meeting between the Sponsor and DNP on 7/22/10, it was agreed that it was acceptable to demonstrate preclinical safety of the Sponsor's product by referencing the FDA's previous findings of safety as found in the approval of NDA 021872, levetiracetam injection, IV infusion, 500mg/5mL, the RLD. Based upon this, the Sponsor has confirmed that the degradation and impurity profile of their product is the same as the RLD, Keppra Injection. Additionally, the Sponsor's review of the published literature has confirmed that no new significant data has been published.

## 5. Clinical Pharmacology/Biopharmaceutics

The following table is submitted by the Sponsor to compare the three formulations of their product with the RLD formulation.

Ingredient	RLD Formulation / 5mL Vial	Proposed 500 mg/ 100mL Bag	Proposed 1000 mg/ 100mL Bag	Proposed 1500 mg/ 100mL Bag
Levetiracetam	500 mg	500 mg	1000 mg	1500 mg
Sodium chloride	45 mg	820 mg	750 mg	540 mg
Glacial acetic acid	-	5.5 mg	6.5 mg	7.5 mg
Sodium acetate trihydrate	8.2 mg	164 mg	164 mg	164 mg
<sup>(b) (4)</sup> Glacial acetic acid	pH adjuster	pH adjuster	pH adjuster	pH adjuster
Water				<sup>(b) (4)</sup>
Buffered at pH	5.5	5.5	5.5	5.5
Diluents -Sodium chloride 0.9% -Lactated Ringers' solution -Dextrose 5%	Qs to 100 mL prior to use	NA	NA	NA

The present label indicates that levetiracetam is rapidly absorbed after oral ingestion (T<sub>max</sub> is 1.3 hours) and readily and rapidly enters the brain compartment. Its bioavailability is >95%. It is not protein bound and it has a volume of distribution of 0.5-0.7 L/kg. Serum concentrations increase linearly over the clinically relevant dosage range of 500- 5000 mg. There is no evidence that the drug accumulates during chronic dosing, and steady-state concentrations are achieved within 24-48 h.

Pharmacokinetic studies of levetiracetam have been conducted in healthy volunteers, in adults, children and elderly patients with epilepsy, and in patients with renal and hepatic impairment. Co-ingestion of food slows the rate but not the

extent of absorption. The elimination half-life in adult volunteers, adults with epilepsy, children with epilepsy and elderly volunteers is 6-8, 6-8, 5-7 and 10-11 hours, respectively. Approximately 34% of a levetiracetam dose is metabolized and 66% is excreted in urine, un-metabolized. The metabolism is not hepatic but occurs primarily in blood by hydrolysis. Autoinduction is not a feature. Clearance is renal in nature it is directly dependent on creatinine clearance. Consequently, dosage adjustments are necessary for patients with moderate to severe renal impairment.

Because its metabolism does not involve enzymes of the cytochrome P450 system, levetiracetam neither induces nor inhibits the enzymes involved in hepatic drug metabolism and appears to be free from pharmacokinetic interactions with other antiepileptic drugs or other non-epilepsy drugs. No clinically relevant pharmacokinetic interactions between other AEDs and levetiracetam have been identified. Similarly, levetiracetam does not interact with digoxin, warfarin and the low-dose contraceptive pill.

The Sponsor has requested a biowaiver. This request was reviewed by Dr. A. Dorantes. The reviewer recommended that the biowaiver be granted. As a result, no new pharmacokinetic studies have been performed.

## 6. Clinical Microbiology

Dr. Vinayak Pawar has completed his microbiology review and had approved this NDA pending resolution of 2 deficiencies. The first relates to drug product specification for endotoxin limits which needed to be lowered. The second is regarding [REDACTED] (b) (4). The data from nine registration batches is insufficient to assure that succeeding batches will consistently meet the required critical control parameters.

The Sponsor has responded to these deficiencies and Dr. Pawar has accepted their response with no further information needed for Clinical Microbiology to fully approve this NDA.

## 7. Clinical/Statistical - Efficacy

The clinical pharmacology requirements of this NDA are met by the Division's previous determination of safety and efficacy, as demonstrated by approval of levetiracetam injection concentrate for infusion, for the same indications as that proposed for the Sponsor's injection, ready-to-infuse solution.

A biowaiver request is based upon the Sponsor's discussions with the FDA during the pre-NDA meeting of July 22, 2010. The waiver has been approved (see above). Requirements of this section are met by reference to the FDA's

approval of the RLD, NDA 21872, for Keppra Injection. Additionally, this assessment is supplemented by the review of published literature revealing that there is no new information that would question the FDA's approval of NDA 21872 or would require modification to the current approved package insert for the RLD.

There are no excipient or diluent formulation differences of the Sponsor's levetiracetam injection formulation which are expected to alter the PK and PD profile of levetiracetam as compared to the RLD Keppra injection formulation.

Based on these scientific findings, HQ Specialty Pharma has been granted a waiver of bioavailability or bioequivalence in accordance with the provisions of 21 CFR§320.22(d) 3. HQ Specialty Pharma intends to rely on the Agency's previous finding of safety and effectiveness of the clinical studies described in NDA 21872 and NDA 21035 for Keppra Injection and tablet as the sole source of clinical data to support its Levetiracetam injection, ready-to-infuse solution.

## 8. Safety

Based upon the discussions with the FDA during the pre-NDA meeting of July 22, 2010, requirements of this section are met by reference to the FDA's approval of RLD NDA 21872 for Keppra injection. Additionally, this assessment is supplemented by the review of published literature which has ensured that there are no new adverse safety concerns beyond those addressed during review and approval of RLD NDA 21872 and any later amended changes.

## 9. Advisory Committee Meeting

None

## 10. Pediatrics

None

## 11. Other Relevant Regulatory Issues

Lubna Merchant performed the DMEPA review and noted: "The use of the established product name [REDACTED] (b) (4)

[REDACTED] For this reason the

established name “levetiracetam in sodium chloride injection” was recommended to the Sponsor. The Sponsor accepted this change. This product does not have a proprietary name.

## 12. Labeling

Based upon the discussions with the FDA during the pre-NDA meeting of July 22, 2010, requirements of this section are met by reference to the FDA’s approval of RLD NDA 21872 for Keppra injection. Additionally, this assessment is supplemented by the review of published literature ensuring that there is no new information that would question the FDA’s approval of NDA 21872 or would require modification to the current approved package insert for the RLD. According to the Keppra package insert, all efficacy trials utilized oral formulations. The recommendation for the parenteral formulation is based upon these studies as well as the demonstration of comparable bioavailability of the oral and the parenteral formulations.

Minor changes in labeling regarding dosing and product information appropriate to the drug product, was made in the label (refer to final label in the approval letter).

## 13. Recommendation on Regulatory Action

I recommend approval for Levetiracetam injection, (b) (4) as an antiepileptic drug indicated for adults (16 years and older) with partial onset seizures, myoclonic seizures (in patients with juvenile myoclonic epilepsy) and primary generalized tonic-clonic seizures when oral administration is temporarily not feasible.

There are no recommendations for Postmarketing Actions, Risk Management Activity or Required Phase 4 Commitments.

**Martin S. Rusinowitz, MD**  
**Medical Reviewer**  
**Division of Neurology Products**

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11/07/2011

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