

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202543Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 2, 2011

FROM: David J. Claffey, Ph.D., ONDQA

SUBJECT: **Final CMC recommendation for**
NDA 202-543, Levetiracetam in Sodium Chloride Injection

At the completion of CMC Review #1 for NDA 202-543 an approval recommendation was made pending the receipt of approval recommendation from the microbiological review. This approval recommendation was received from Dr. Vinayak Pawar on 14 OCT 2011.

Further discussions regarding the (b) (4) and (b) (4) statements on the container labels after completion of CMC Review #1 resulted in the Applicant agreeing to delete these statements at next label printing. Examples of the revised labels are attached to this memo. They are acceptable from a CMC perspective.

An approval recommendation can now be made from a CMC perspective.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DAVID J CLAFFEY
11/04/2011

RAMESH K SOOD
11/04/2011

NDA 202-543

Levetiracetam in Sodium Chloride Injection

HQ Specialty Pharma

Review #1

**David J. Claffey, PhD
ONDQA**

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Chemistry Review Data Sheet

1. NDA 202-543
2. REVIEW #:1
3. REVIEW DATE: 25 AUG 2011
4. REVIEWER: David J. Claffey, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

IND 108,762

Document Date

5 MAY 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

N-000

N-001

N-004

N-005

Document Date

13 JAN 2011

26 APR 2011

3 AUG 2011

18AUG 2011

7. NAME & ADDRESS OF APPLICANT:

Name:

HQ Specialty Pharma LLC

Address: 120 Route 17 North, Suite 130, Paramus NJ 07653

Representative:

Joseph Pizza

Chemistry Review Data Sheet

Telephone:

201 857 8290

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None proposed
- b) Non-Proprietary Name (USAN): levetiracetam injection
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type:
 - Submission Priority:

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

RLD: Keppra Injection (NDA 21-872)

10. PHARMACOL. CATEGORY: Antiseizure

11. DOSAGE FORM: Injection

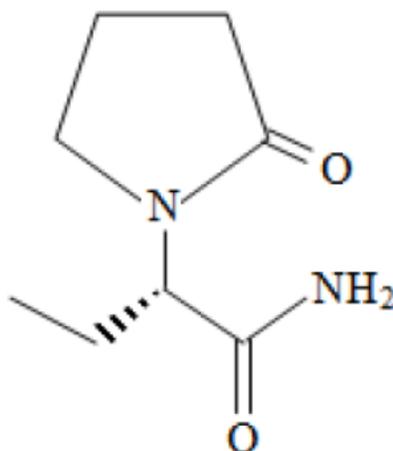
12. STRENGTH/POTENCY: 500 mg/100 mg (5mg/ml), 1000 mg/100 ml (10 mg/ml) and 1500 mg/100 ml (15 mg/ml)

13. ROUTE OF ADMINISTRATION: Intravenous Infusion

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet



Molecular formula : C₈H₁₄N₂O₂

Molecular weight : 170.21

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)		(b) (4)	Levetiracetam	3	Adequate	15 JUN 2011	
			(b) (4)	4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

Chemistry Review Data Sheet

- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
ONDQA Biopharm	Biowaiver Request Granted	29 SEP 2011	Angelica Dorantes, PhD
EES	Overall Acceptable		
Pharm/Tox	None		
Biopharm	None		
EA	N/A		
Microbiology	None		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 202-543

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval from a CMC perspective pending receipt of an approval recommendation from the microbiological reviewer.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Levetiracetam is a white crystalline powder which melts at 116-119°C. It is very soluble in water and stated to be freely soluble in chloroform, methanol and ethanol. Levetiracetam corresponds to the s-configuration and has a specific optical rotation of (b)(4). No polymorphs are known. Much of the drug substance CMC information is referred to the manufacture's master file (DMF (b)(4)). Adequate characterization data was provided in the application. The drug substance specification, including its impurity controls, are in line with the USP monograph for levetiracetam and ICH Q3C limits for (b)(4). CoAs were provided on three drug substance lots which were tested by both the drug substance and drug product manufacturer. The results were all well within specified limits and were comparable to each other. The stability data in the drug substance master file support a (b)(4) retest date.

Drug Product: The drug product is a 100ml premixed ready-to-infuse solution of levetiracetam of three strengths - 500 mg (5mg/ml), 1000 mg (10 mg/ml) and 1500 mg (15 mg/ml). The solutions are packaged in (b)(4) bags referred to as (b)(4) bags - these contain two administration tubing ports, one closed by a twist off port with (b)(4) cap and the other one closed by the injection port with break open cap. The bag contains an aluminum overwrap. The product contains compendial excipients - WFI, sodium chloride and acetate buffering agents. Development initially aimed at producing a single strength product (500 mg/100 ml) which would be identical to the reference listed drug (RLD) 500 mg/ 5 ml levetiracetam (KEPPRA Injection, NDA 21-872) after the latter product's constitution in 100 ml of 0.9% saline. During the review cycle of this application, two other strengths were added to the application, 1000 mg/ 100 ml and 1500 mg/100 ml. All three strengths have the same volume (100 ml).

Executive Summary Section

The proposed product contains the same excipients as Keppra Injection (RLD). It also has the same route of administration, dosing regimen (frequency and duration) as the RLD when diluted. Drug product development studies aimed at matching the characteristics of the RLD after its dilution in 0.9% NaCl. Of critical concern was the drug product stability both on storage and during (b) (4). Studies demonstrated the solution's relative robustness with only minor increases being observed in the known (b) (4). Manufacturing development studies adequately addressed the concerns over the robustness of the drug product to minor changes in the manufacturing process and environment (b) (4).

Drug product manufacture, testing (chemical and microbial release and stability) and packaging will be performed at (b) (4). As expected for the proposed product, a relatively non-complex manufacturing process was developed, involving (b) (4).

Microbial control is via (b) (4).

The drug product specification is typical of a parenteral drug product. Batch analysis data for three pilot-scale registration batches of each strength were provided. All batches met the proposed limit with little variation between batches. The container closure system consists of 100 ml dual-port (b) (4) bags (b) (4) (b) (4) bags). The bags are individually packaged in an aluminum overwrap and (b) (4). CoAs were provided for the container closure components. The container met compendial physiochemical and extractable test requirements. A toxicological assessment on the extractables was carried out with no "toxicological risks from leachable substances" found.

Drug product stability data was provided (N-002) on three lots of each strength. Six months accelerated data was provided on each lot; 12 months long-term storage data on the lowest strength and nine months each on the other two strengths. Each lot was pilot-scale (b) (4) commercial) and used the commercial site and process. No significant changes occurred thus-far with exception of minor increases in the (b) (4). The data support the proposed 24-month expiry period for storage at controlled room temperature. "Bridging Studies" and physical drug-drug compatibility studies were conducted to support the addition of the RLD and (b) (4) other antiepileptic drugs, respectively to the proposed ready-to-infuse drug product. The results of these studies met the established test criteria - as did a thermal cycle study (-20°C, 25°C and 40°C).

CDER Labeling and Nomenclature Committee recommended that the established name be in the following format: "Levetiracetam in 0.xx% Sodium Chloride Injection" i.e.:

Levetiracetam in 0.82% Sodium Chloride Injection (500 mg/100 ml)

Levetiracetam in 0.75% Sodium Chloride Injection (1000 mg/100 ml)

Levetiracetam in 0.54% Sodium Chloride Injection (1500 mg/100 ml)

The use of a proprietary name has not been proposed.

Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

The drug product is intended as a single-use, ready-to-use for intravenous infusion over 15 minutes. It should be stored at 20° to 25°C (68° to 77°F) (b) (4)
(b) (4) Data provided in the application support a 24 month expiry period.

C. Basis for Approvability or Not-Approval Recommendation

DMF (b) (4) for the drug substance CMC data was found to be adequate by Kandasamy Subburaj on 12 JAN 2011. The drug product information was found to be adequate. An overall “acceptable” recommendation was provided from CDER Office of Compliance on 17 AUG 2011. The biowaiver request was granted by ONDQA Biopharmaceutics reviewer Dr. Angelica Dorantes on 29 AUG 2011.

At completion of this review an approval recommendation from a CMC perspective will be made pending an approval recommendation from the microbiological reviewer.

III. Administrative**A. Reviewer’s Signature****B. Endorsement Block**

ONDQA/DClaffey
ONDQA/RSood
ONDQA/MHeimann
ONDQA/TBouie
HFD-120/JWare

C. CC Block

68 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DAVID J CLAFFEY
09/08/2011

RAMESH K SOOD
09/09/2011

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division: Division of Neurology Products
NDA: 202543
Applicant: HQ Pharma
Stamp Date: 13-Jan-2011
PDUFA Date: 13-Nov-2011
Trademark:
Established Name: Levetiracetam Injection
Dosage Form: Injection
Route of Administration: IV
Indication: Epilepsy

CMC Lead: Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Summary and Critical Issues:

Summary

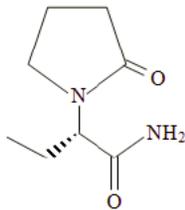
Levetiracetam is currently marketed by UCB Pharma under the tradename Keppra®. It is approved for use as adjunctive therapy in the treatment of partial onset seizures, treatment of myoclonic seizures, and treatment of primary generalized tonic-clinic seizures. Four dosage forms are available, i.e., conventional immediate release tablets (NDA 21-035), oral solution (NDA 21-505), injection (NDA 21-872), and extended release tablets (NDA 22-285). The approved parenteral formulation is available as a 5 mL vial containing 100 mg/ mL levetiracetam in acetate buffered sodium chloride solution. Keppra Injection must be diluted in 100 mL of a compatible diluent (0.9% Sodium Chloride, Lactated Ringer's solution, or 5% Dextrose) prior to i.v. administration.

In the current NDA, which is submitted as a 505(b)(2) application referencing NDA 21-872, HQ Pharma proposes to market a ready-to-infuse version of levetiracetam injection. The proposed product is a 500 mg/100 mL parenteral solution packaged in a (b) (4) infusion bag. The product is stated to be equivalent to 5 mL of Keppra Injection diluted in 0.9% saline.

Drug Substance

The active ingredient, levetiracetam (chemical name: (S)-(-)- α -2-oxo-1-pyrrolidine acetamide), is a well characterized small molecule with molecular formula $C_8H_{14}N_2O_2$ and molecular weight 170.21. The bulk drug substance is described as a white crystalline powder that is very soluble in water and freely soluble in chloroform, methanol and ethanol.

Levetiracetam has one chiral center with the absolute S-configuration. The chemical structure is:



The bulk drug substance is manufactured by (b) (4)

Information related to the manufacture of levetiracetam is incorporated by cross reference to the manufacturer's DMF (b) (4). The DMF was most recently reviewed and found adequate by K. Subbaraj (review dated 12-Jan-2011).

The drug product manufacturer's specification is provided in the application (applicant's **Table 3.2.S.4.1-1**). The specification is based on the USP monograph for Levetiracetam. The USP monograph is referenced for analytical procedures and provided in the NDA. Method validation reports are included in the application.

Table 3.2.S.4.1-1

Test	Limits	Analytical Procedure
Appearance	White crystalline powder	Visual
Identification A IR	Positive	USP <197K>
Identification B HPLC	Positive	USP
Moisture Content	≤ 0.5%	USP <921> Method Ia
Residue on Ignition	≤ 0.1%	USP <281>
Heavy Metals	≤ 20 ppm	USP <231> Method II
Levetiracetam R-enantiomer***	≤ 0.8%	USP
(b) (4)		
Any Individual Unspecified Impurity	≤ 0.05 %	USP
Total Impurities	≤ 0.4 %	USP
(b) (4)		

*** Proposed specifications are consistent with the USP monograph. Internal API specifications were established prior to publication of the USP monograph and may not be identical to the above specifications.

Drug Product

The composition of ready-to infuse Levetiracetam Injection is given in the applicant's **Table 3.2.P.1-2: Composition of Levetiracetam Injection**. All excipients are commonly used in parenteral products and are stated to conform to compendial requirements.

Table 3.2.P.1-2: Composition of Levetiracetam Injection

Name of Ingredients	Composition		Amount per Batch (L)	
	mg /mL	mg per 100 mL container	Exhibit Batch Size (Pilot Scale)	Proposed Commercial Batch Size
Levetiracetam *	5.0	500	(b) (4)	(b) (4)
Sodium Chloride	8.2	820		
Glacial Acetic Acid	0.055	5.5		
Sodium Acetate Trihydrate	1.64	164		
(b) (4) Glacial Acetic Acid	(b) (4)			
WFI				
Total	1 mL	100 mL		
Theoretical Number of Containers	NA	1		

*The quantity of Levetiracetam API that is weighed is calculated as follows:
 Kg as potency "on as is basis" = 5 Kg * Assay (on anhydrous basis) * (100-Water content)/100



It is noted that no clinical efficacy or clinical pharmacology studies were performed to support the proposed commercial formulation. The applicant has included a request for waiver of *in vivo* bioavailability/bioequivalence studies in Module 1.12.15.

The Pharmaceutical Development reflects an empirical approach to formulation and process development. E.g., the applicant summarizes the approach to product development as:

1. Characterization of the drug substance, Levetiracetam
2. Assessment of the RLD, KEPPRA Injection formulation
3. Development of premix formulation based on the RLD formulation that is sterile buffered, iso-osmolal, and stable at room temperature
4. Demonstration of the premix formulation stability at accelerated and room temperature
5. Manufacture of NDA registration batches and packaging in the desired container closure system
6. Conduct of accelerated and long term room temperature stability studies to support shelf life stability

Reviewer comment: Despite the applicant's summary of the development process, the pharmaceutical development section is reasonably detailed given the relatively simple formulation.

The drug product will be manufactured by [REDACTED] (b) (4) The manufacturing process is relatively simple and consists of:

[REDACTED] (b) (4)

The NDA stability package is limited to 6 months long-term and accelerated stability data for three pilot scale batches. The sponsor requests that a 24 month expiry be assigned.

Critical issues for review

Drug Substance

No critical issues were identified during the initial assessment.

Drug Product

Levetiracetam is relatively stable; however, it is susceptible to [REDACTED] (b) (4) [REDACTED] The reviewer should consult with the Pharm/Tox reviewer to determine whether this degradant has been adequately qualified.

Additional issues

Administrative: A claim for categorical exclusion from environmental assessment is included in Module 1.

Establishment Evaluation: The firm provided full information for the manufacturer of [REDACTED] (b) (4) [REDACTED] All facilities were submitted in EES on 01-Feb-2011. [Refer to Attachment 1.]

Labeling/Established Name: The active ingredient, Levetiracetam, is a neutral molecule. Thus, there are no conflicts between the stated potency, 500 mg/100 mL, and the established name, Levetiracetam Injection.

Microbiology: The drug product is [REDACTED] (b) (4) small volume parenteral. A Micro consult was sent on 26-Jan-2011.

Comments for 74-Day Letter

There are no comments for the 74 day letter.

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective. The product is relatively simple and the drug substance DMF has been reviewed and found adequate. There are no QbD aspects. Assignment of the CMC portion of the NDA to a single reviewer is recommended. The sponsor has requested a biowaiver for the commercial formulation. Therefore, a Biopharmaceutics review will be needed. Due to the simplicity of the product and manufacturing process this application is not recommended for an office-level or division level regulatory briefing.

Martha R. Heimann, Ph.D.
CMC Lead

2/4/2011
Date

Ramesh Sood, Ph.D.
Branch Chief

2/4/2011
Date

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 202543/000	Sponsor:	HQ SPECIALITY PHARMA
Org. Code:	120		120 ROUTE 17 NORTH
Priority:	3		PARASMUS, NJ 07652
Stamp Date:	13-JAN-2011	Brand Name:	Levetiracetam
PDUFA Date:	13-NOV-2011	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	14-SEP-2011	Product Number; Dosage Form; Ingredient; Strengths	001; SOLUTION, INJECTION; LEVETIRACETAM; 500MG/100ML

FDA Contacts:	T. BOUIE	Project Manager	301-796-1649
	D. CLAFFEY	Review Chemist	301-796-1343
	M. HEIMANN	Team Leader	301-796-1678

Overall Recommendation:

Establishment:	CFN:	FEI:	(b) (4)	
			(b) (4)	
DMF No:				AADA:
Responsibilities:	FINISHED DOSAGE MANUFACTURER			
	FINISHED DOSAGE PACKAGER			
	FINISHED DOSAGE RELEASE TESTER			
Profile:			(b) (4)	OAI Status: NONE
Last Milestone:	SUBMITTED TO DO			
Milestone Date:	01-FEB-2011			

Establishment:	CFN:	FEI:	(b) (4)	
			(b) (4)	
DMF No:				AADA:
Responsibilities:	DRUG SUBSTANCE MANUFACTURER			
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS			
Last Milestone:	OC RECOMMENDATION			
Milestone Date:	01-FEB-2011			
Decision:	ACCEPTABLE			
Reason:	BASED ON PROFILE			

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: SUBMITTED TO DO

Milestone Date: 01-FEB-2011

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR A NEW NDA/BLA**

NDA Number: 201-543

Applicant: HQ Pharma, Inc.

Stamp Date: 13-Jan-2011

Drug Name: Levetiracetam Injection

NDA Type: Standard

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	x		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		Additional facility information was requested and provided by applicant
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		Categorical exclusion requested
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		Cross-reference to DMF (b) (4)
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	N/A		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	N/A		No clinical trials were performed to support NDA.
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	X		Fileability to be determined by Microbiology reviewer

IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Martha R. Heimann, Ph.D.

2/4/2011

Pharmaceutical Assessment Lead, DNDQA 1, ONDQA

Date

Ramesh Sood, Ph.D.

2/4/2011

Branch Chief, DNDQA 1, ONDQA

Date

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/s/

MARTHA R HEIMANN
02/04/2011

RAMESH K SOOD
02/04/2011