CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-505

CHEMISTRY REVIEW(S)

NDA 21-505

Keppra (levetiracetam) Oral Solution 100 mg/mL

UCB Pharma, Inc.

Thomas A. Broadbent, Ph.D.
Division of Neuropharmacological Drug Products

Table of Contents

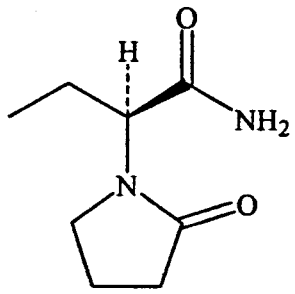
Chemistry NDA Review Data Sheet

1. **NDA # 21-505**

2. **REVIEW #:** 2

3. **REVIEW DATE:** 09-JUL-2003

4. **REVIEWER:** Thomas A. Broadbent, Ph.D.



5. **PREVIOUS DOCUMENTS**

Previous Documents	**Document Date**
T-con (5 total)	(01-AUG-2002) (08-OCT-2002) (14-MAR-2003) (10-APR-2003) (09-JUL-03)
CMC Review # 1	14-APR-03

6. **SUBMISSIONS BEING REVIEWED:**

Submissions Reviewed	**Document Date**
Amendment of original NDA	21-MAY-2003

7. **NAME & ADDRESS OF APPLICANT:**

Name: UCB Pharma, Inc.
Address: 1950 Lake Park Drive, Smyrna, GA 30080

Representative: Patricia Fritz
Telephone: (770) 437-5554

Contact for CMC Issues: Mary Alonso
Telephone: (770) 970-8580

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary Name: Keppra® Oral Solution
   b) Non-Proprietary Name (USAN): levetiracetam

   c) Code Name / # ucb L059
   d) Chem. Type/Submission Priority
      Chem. Type = 3
      Submission Priority = S

9. **LEGAL BASIS FOR SUBMISSION:** N/A

10. **PHARMACOLOGICAL CATEGORY:** Adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy

11. **DOSAGE FORM:** Oral Solution

12. **STRENGTH / POTENCY:** 100 mg / mL

13. **ROUTE OF ADMINISTRATION:** oral

14. **Rx / OTC DISPENSED:** XXX **Rx** __ **OTC**

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)**
Not Applicable

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

Chemical Name: (-)-(*S*)-α-ethyl-2-oxo-1-pyrrolidineacetamide
Formula: $C_8H_{14}N_2O_2$
Formula Weight: 170.21

17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE (1)	STATUS (2)	DATE REVIEW COMPLETED	COMMENTS
[redacted]	2	[redacted]	[redacted]	1	Adequate	7/26/02	
[redacted]	3	[redacted]	[redacted]	4	N/A	--	Information in NDA
[redacted]	3	[redacted]	[redacted]	3	Adequate	8/12/99	
[redacted]	3	[redacted]	[redacted]	3	Adequate	7/30/01	
[redacted]	3	[redacted]	[redacted]	4	N/A	--	Information in NDA
[redacted]	3	[redacted]	[redacted]	4	N/A	--	Information in NDA
[redacted]	3	[redacted]	[redacted]	3	Adequate	11/05/98	
[redacted]	3	[redacted]	[redacted]	3	Adequate	3/08/99	
[redacted]	3	[redacted]	[redacted]	3	Adequate	4/30/02	
[redacted]	3	[redacted]	[redacted]	3	Adequate	2/14/03	
[redacted]	3	[redacted]	[redacted]	4	N/A	--	Information in DMF [redacted] & NDA
[redacted]	3	[redacted]	[redacted]	4	N/A	--	Information in DMF [redacted]
[redacted]	3	[redacted]	[redacted]	3	Adequate	2/23/01	
[redacted]	3	[redacted]	[redacted]	4	N/A	--	Information in NDA
[redacted]	3	[redacted]	[redacted]	3	Adequate	9/15/00	
[redacted]	3	[redacted]	[redacted]	3	Adequate	9/27/00	
[redacted]	3	[redacted]	[redacted]	3	Adequate	3/22/01	

(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
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
IND	45,151	Development of Keppra Tablets & Oral Solution
NDA	21-035 (AP 30-NOV-99)	Levetiracetam DS & Keppra Tablets

18. **STATUS:**

CONSULTS / CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A	--	--
EES	Acceptable	19 December 2002	Shirnette Ferguson
Pharm/Tox	Approval	14 April 2003	Ed Fisher
Biopharm	Approval	2 April 2003	Kofi Kumi
LNC	N/A	--	--
Methods Validation	Pending	Pending	Thomas Broadbent
ODS/DSRCS	Comments to DNPDP	9 April 2003	Janine Best
EA	Adequate	31 October 2002	Florian Zielinsky
Microbiology	Approval	17 January 2003	Vinayak Pawar
DMETS	Comments to DNPDP	2 April 2003	Marci Lee

APPEARS THIS WAY ON ORIGINAL

Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

APPROVAL of NDA 21-505 is recommended from a CMC perspective. The sponsor has revised the NDA to include a recommendation for an additional in-process control [redacted] and a commitment to update European Pharmacopoeia methods included in the NDA by prior approval supplements. Two changes in labeling concerning CMC have been effected in the current draft of insert labeling; one is according to recommendation and the other is a deleted listing of a coloring agent for Keppra Tablets (adequate for NDA 21-035).

B. Recommendation on Phase 4 (Post-Marketing) Commitments and Risk Management Steps

No phase 4 commitments

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Keppra® Oral Solution is a grape-flavored, alcohol-free and sugar-free aqueous solution. The solution is non-sterile, with microbiological limits for total viable count (NMT [redacted] and *Salmonella* and *E. coli* (negative). Methyl paraben and propyl paraben are ingredients as preservatives. The pH range of the solution is specified as [redacted] The solution API concentration is 100 mg/mL or 1500 mg per 15 mL, the typical dose. [redacted] The commercial product is packaged in 16 oz glass and HDPE bottles (labeled amount 475 mL). The solution can become discolored in light, but the packaging provides adequate protection from light.

Levetiracetam (USAN, INN & BAN) is a white to off-white crystalline powder with a faint odor. Description of the chemistry, manufacturing and control of the drug substance (ucb L059) is provided in NDA 21-035, Keppra Tablets. It is very soluble in water; the limit of solubility is approximately 104 g per 100 mL of water. Particle size and crystal aggregation are not relevant to this application because the product is provided as a solution. (Differences in these physical characteristics have been observed for different synthetic routes.) The retest period of the bulk drug substance is [redacted] The [redacted] impurities of the drug product are [redacted]

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

Keppra is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. The recommended initial treatment is 500 mg *BID*. Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg.
Expiration dating: 24 months is proposed. The reviewer concurs.
Recommended storage condition: 25°C (77°F); excursions permitted to 15-30° (59-86°F)
[See USP Controlled Room Temperature]

C. Basis for Approvability or Not-Approval Recommendation

Approval was recommended in CMC Review # 1. The CMC provisions of the amended submission are according to recommendations or are minor in nature. They do not change the recommendation for approval.

III. Administrative

A. Reviewer's Signature
Electronic signature in Division File System

B. Endorsement Block
See Division File System

C. CC Block
Thomas Broadbent, CMC Reviewer, HFD-120
Maryla Guzewska, Neurology CMC Team Leader, HFD-120
Melina Griffis, Project Manager, HFD-120

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/s/

Thomas Broadbent
7/14/03 02:10:32 PM
CHEMIST

Maryla Guzewska
7/14/03 02:13:04 PM
CHEMIST

NDA 21-505

Keppra (levetiracetam) Oral Solution 100 mg/mL

UCB Pharma, Inc.

Thomas A. Broadbent, Ph.D.
Division of Neuropharmacological Drug Products

Table of Contents

Index of Review Tables Page

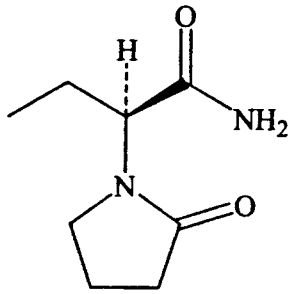
Chemistry NDA Review Data Sheet

1. **NDA #** 21-505

2. **REVIEW #:** 1

3. **REVIEW DATE:** 14-APR-2003

4. **REVIEWER:** Thomas A. Broadbent, Ph.D.



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Amendment	09-APR-2003

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8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary Name: Keppra® Oral Solution
   b) Non-Proprietary Name (USAN): levetiracetam

   c) Code Name / # ucb L059
   d) Chem. Type/Submission Priority
      Chem. Type = 3
      Submission Priority = S

9. **LEGAL BASIS FOR SUBMISSION:**

Section 505(b) of the Federal Food, Drug, and Cosmetic Act

10. **PHARMACOLOGICAL CATEGORY:** Adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy

11. **DOSAGE FORM:** Oral Solution

12. **STRENGTH / POTENCY:** 100 mg / mL

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LNC	N/A	--	--
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Microbiology	Approval	17 January 2003	Vinayak Pawar
DMETS	Comments to DNPDP	2 April 2003	Marci Lee

APPEARS THIS WAY
ON ORIGINAL

Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

APPROVAL of NDA 21-505 is recommended from a CMC perspective.

The action letter should include a reminder of the sponsor's commitments.

1. UCB will provide updates for *European Pharmacopoeia* methods included in ingredient and product specifications by CBE supplements.
2. In-process range limits will be established for the [redacted]
3. A methods validation package will be provided for the ID, drug assay & related substance HPLC method.

B. Recommendation on Phase 4 (Post-Marketing) Commitments and Risk Management Steps

No phase 4 commitments

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Keppra® Oral Solution is a grape-flavored, alcohol-free and sugar-free aqueous solution. The solution is non-sterile, with microbiological limits for total viable count (NMT [redacted]) and *Salmonella* and *E. coli* (negative). Methyl paraben and propyl paraben are ingredients as preservatives. The pH range of the solution is specified as [redacted] The solution API concentration is 100 mg/mL or 1500 mg per 15 mL, the typical dose. [redacted] The commercial product is packaged in 16 oz glass and HDPE bottles (labeled amount 475 mL). The solution can become discolored in light, but the packaging provides adequate protection from light.

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Expiration dating: 24 months is proposed. The reviewer concurs.
Recommended storage condition: 25°C (77°F); excursions permitted to 15-30° (59-86°F)
[See USP Controlled Room Temperature]

C. Basis for Approvability or Not-Approval Recommendation

CMC provisions warrant approval. The applicant has adequately documented the composition of the product, control of the ingredients, the manufacturing process, and the release of the product. Stability data are adequate to support the proposed expiration period of 24 months. Establishment evaluation has been completed and an overall acceptable compliance recommendation was received (19 December 2002).

III. Administrative

A. Reviewer's Signature

Electronic signature in Division File System

B. Endorsement Block

See Division File System

C. CC Block

Thomas Broadbent, CMC Reviewer, HFD-120
Maryla Guzewska, Neurology CMC Team Leader, HFD-120
Jackie Ware, Project Manager, HFD-120
Melina Griffis, Project Manager, HFD-120

29 Page(s) Withheld

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/s/

Thomas Broadbent
4/14/03 05:47:05 PM
CHEMIST

Maryla Guzewska
4/15/03 07:39:29 AM
CHEMIST