# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-285**

# CHEMISTRY REVIEW(S)

## CMC BRANCH CHIEF MEMORANDUM

| | |
|---|---|
| **To:** | NDA 22-285 |
| **From:** | Ramesh Sood, Ph.D., Branch Chief, ONDQA |
| **Date:** | 15-Aug-2008 |
| **Drug:** | Keppra (levetiracetam) extended-release Tablets |
| **Route of administration:** | Oral |
| **Strength:** | 500 mg |
| **Subject:** | **"Complete Response"** recommendation for NDA [redacted] b(4) |

---

**Introduction:** Levetiracetam (chemical name: (S)-(-)-α-2-oxo-1-pyrrolidine acetamide) is currently approved for use as adjunctive therapy in the treatment of partial onset seizures, treatment of myoclonic seizures, and treatment of primary generalized tonic-clonic seizures. This application is for an extended-release tablet formulation of levetiracetam. Currently, three dosage forms of this drug are available, i.e., conventional immediate release tablets (250 mg, 500 mg, 750 mg and 1000 mg), oral solution (100 mg/mL), and injection (100 mg/mL). The current NDA provides for a 500 mg levetiracetam extended-release tablet formulation for adjunctive treatment of partial onset seizures in patients [redacted] years of age or older. The extended release formulation would allow for a reduction in dosing frequency to once daily. The drug product will be supplied for oral administration as oblong, white film-coated extended-release tablets with red imprinting in bottles [redacted] b(4) b(4)

**Drug Substance:** The drug substance, levetiracetam, is a water soluble single (S-) enantiomer. It is known to be stable in slightly acidic aqueous media, such as that proposed in the drug product dissolution test. All CMC information regarding levetiracetam is cross referenced to the approved NDA 21-035 (Keppra Tablets). The release specifications for levetiracetam are equivalent to those in the cross referenced application. The retest date for levetiracetam is [redacted] based on ICH stability data provided to the cross referenced application. b(4)

**Drug product:** The tablet [redacted] is composed of [redacted] hypromellose. The [redacted] is comprised of silica, PEG and [redacted] The hypromellose confers the [redacted] and is currently approved for use in similar quantities in the cross-referenced immediate release tablet. It has no effect on the drug release properties. All inactive ingredients have been previously used in CDER approved products. The product manufacturing includes [redacted] The manufacturing in-process controls include uniformity of mass, hardness, friability and appearance. The quality of the product is further controlled through final product specification that includes appearance, identification (achiral and chiral HPLC), uniformity of dosage units, drug release, assay, impurities and water content. All analytical methods used in the product analysis have been adequately described and validated. b(4)

A 24-month expiration date has been assigned to the product based on the provided stability data when stored at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F).

**An overall recommendation for the acceptability of the manufacturing sites is pending from the Office of Compliance at the time of writing this memorandum.**

**Recommendation:** All CMC related issues had been resolved for this application. The final "Approval" recommendation from CMC perspective will be made via the final memorandum by the reviewer once the Office of Compliance has provided a final acceptable recommendation for the manufacturing sites.

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

Ramesh Sood
8/15/2008 04:29:12 PM
CHEMIST

# NDA 22-285

## Keppra XR
## levetiracetam extended-release tablets

## UCB, Inc

## Review #2

**David J. Claffey, PhD**
**ONDQA**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 22-285

2. REVIEW #2

3. REVIEW DATE: 11 AUG 2008

4. REVIEWER: David J. Claffey, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original Application | 28 JAN 2008 |
| Information Request | 21 MAY 2008 |
| Review #1 | 14 MAY 2008 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Amendments | 30 JUN 2008 |
| | 15 JUL 2008 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | UCB, INC. |
| Address: | 1950 Lake Park Drive, Smyrna, GA 30080 |
| Representative: | Cassie Buckhalt |
| Telephone: | 770 970 8621 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Keppra XR
b) Non-Proprietary Name (USAN): levetiracetam extended release tablets
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 501 (b) (1)

10. PHARMACOL. CATEGORY: Adjunctive Therapy in the Treatment of Partial Onset Seizures in Adults and Adolescents - years and older with Epilepsy. b(4)

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 500 mg

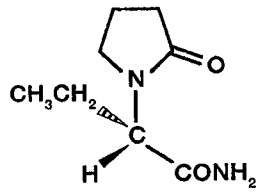
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(S)-(-)-alpha-ethyl-2-oxo-1-pyrrolidine acetamide
$C_8H_{14}N_2O_2$
MW = 170.21




## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | | | | 4 | | | |
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b(4)

[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 | 76,812 | IND for Keppra XR |
| NDA | 21-035 | Keppra Tablets (cross referenced for drug substance information) |
| NDA | 21-505 | Keppra Oral Solution |
| NDA | 21-872 | Keppra Injection |

## 18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| EES | Not complete | | |
| Pharm/Tox | Not complete | | |
| Biopharm | Not complete | | Ta-Chen Wu, PhD |
| EA | FONSI | 25 FEB 2008 | Raanan A. Bloom, PhD |

## 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 22-285

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

All outstanding CMC issues have been resolved. The Office of Compliance has yet to issue an overall recommendation. An approval recommendation from a CMC perspective will be made on receipt of an overall acceptable recommendation from the Office of Compliance.

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

## II. Summary of Chemistry Assessments

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

The drug product will be supplied for oral administration as a single strength (500 mg) oblong, white film-coated extended-release tablets with red imprinting in bottles [redacted] The tablet [redacted] is composed of [redacted] hypromellose. [redacted] is comprised of silica, PEG and [redacted] The hypromellose confers the [redacted] b(4)

[redacted] and is currently approved for use in similar quantities in the cross-referenced immediate release tablet. It has no effect on the drug release properties.

The drug substance is highly water soluble (1 g/ml) with no known polymorphs. The currently marketed immediate-release dosage form has near 100% bioavailability. Development aimed at producing an equivalent extended-release formulation in a reasonably-sized tablet. Three different slow release formulations (F1, F2 and F3) were selected for PK study versus an immediate-release tablet in Study N01140. Subsequent Phase 3 clinical studies used another formulation, F4, which is identical to the proposed commercial formulation with the exception of [redacted] b(4)

The film-coated tablets are manufactured and packaged by UCB Pharma in Brain-L'Alleud, Belgium and the imprinting is carried out at the UCB Farchim SA site in Bulle Switzerland. CDER OC has not yet issued an overall recommendation regarding these sites. An information request was sent to the Applicant on 21 MAY 2008 concerning several aspects of the manufacturing process including control of the hypromellose, blend uniformity and tablet hardness. The subsequent responses of 30 JUN 2008 and 15 JUL 2008 resolved these issues. The drug product dissolution method is adequate and was demonstrated to be discriminatory over a range of hypromellose concentrations.

Data up to 12 months at 25°C/60%RH and 6 months at 40°C/75%RH for the three of the four primary stability lots was provided. These three lots have the same formulation as the commercial lots but contain [redacted] The forth primary stability lot is identical in formulation to the commercial lots [redacted] Three months data is available for this lot at both accelerated and long-term storage conditions. Some supportive stability data (six months) was also provided [redacted] tablets which were used during development. All these lots were manufactured at pilot-scale at the proposed commercial manufacturing site and were packaged in both commercial packaging presentations. All results remained within specified limits and no significant changes were noted thus-far, thus supporting the proposed 24 month expiry period at 25°C/60%RH. b(4)

The drug substance, levetiracetam, is a water soluble single (S-) enantiomer. It is known to be stable in slightly acidic aqueous media, such as that proposed in the drug product dissolution test. All CMC information regarding levetiracetam is cross referenced to the approved NDA 21-035 (Keppra Tablets). The release specifications for levetiracetam are equivalent to those in the cross referenced application. The retest date for levetiracetam is [redacted] based on ICH stability data provided to the cross referenced application. b(4)

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

This application proposes the use of KEPPRA XR™ as adjunctive therapy in the treatment of partial onset seizures in patients [redacted] years of age with epilepsy. b(4)

It is proposed that treatment 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. There is no evidence that doses greater than 3000 mg/day confer additional benefit.

### C. Basis for Approvability or Not-Approval Recommendation

The Applicant provided adequate responses to the Information Requests of 28 JAN 2008 and 21 MAY 2008. An approval recommendation will be made on receipt of an overall acceptable recommendation from the Office of Compliance.

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

DClaffey: Same date as draft review

MHeimann
RSood
SDaugherty

**C. CC Block**

# 6 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Chemistry-* 2

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/s/
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David Claffey
8/15/2008 12:53:25 PM
CHEMIST

Ramesh Sood
8/15/2008 12:56:10 PM
CHEMIST

**MEMORANDUM**

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

**DATE:** September 9, 2008

**FROM:** David J. Claffey, PhD

**SUBJECT:** **Office of Compliance recommendation for NDA 22-285**
NDA 22-285, Keppra XR levetiracetam extended release tablets

The most recent CMC review (15 AUG 2008) for NDA 22-285 recommended that this application be approved on receipt of an overall acceptable recommendation from the Office of Compliance. Such a recommendation was received on 9 SEP 2008 (see Attachment). All outstanding CMC issues have now been resolved. Recommend that this application be approved from a CMC perspective.

# ATTACHMENT
## OC Recommendation

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22285/000
Org Code : 120
Priority : 3S

Stamp Date : 14-NOV-2007
PDUFA Date : 14-SEP-2008
Action Goal :
District Goal: 16-JUL-2008

Sponsor: UCB
NO CITY, , XX

Brand Name : KEPPRA EXTENDED RELEASE TABLETS
Estab. Name:
Generic Name: LEVETIRACETAM
Dosage Form: (EXTENDED-RELEASE TABLET)
Strength : 500MG

| | | | |
|---|---|---|---|
| FDA Contacts: | S. GOLDIE | Project Manager | 301-796-2055 |
| | D. CLAFFEY | Review Chemist | 301-796-1343 |
| | M. HEIMANN | Team Leader | 301-796-1678 |

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Overall Recommendation: ACCEPTABLE on 09-SEP-2008by S. FERGUSON(HFD-322) 301-796-3247

---

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

DMF No: AADA: b(4)

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION

Milestone Date: 09-SEP-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

b(4)

DMF No: AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-MAR-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : 9610703 FEI : 3002808410

UCB BIOPRODUCTS SA

CHEMIN DU FORIEST

BRAINE L'ALLEUD, , BE

DMF No: AADA: 021035

Appears This Way
On Original

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-APR-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION
Profile : TTR OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-JUN-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : FEI : 3005023799
UCB FARCHIM SA
10, CHEMIN DE CROIX BLANCHE
BULLE, , SZ
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER

| | | | |
|---|---|---|---|
| Profile : | CSN | OAI Status: | NONE |
| Last Milestone: | OC RECOMMENDATION | | |
| Milestone Date: | 08-SEP-08 | | |
| Decision : | ACCEPTABLE | | |
| Reason : | DISTRICT RECOMMENDATION | | |
| Profile : | TTR | OAI Status: | NONE |
| Last Milestone: | OC RECOMMENDATION | | |
| Milestone Date: | 08-SEP-08 | | |
| Decision : | ACCEPTABLE | | |
| Reason : | DISTRICT RECOMMENDATION | | |

---

Establishment : CFN : 1314625 FEI : 1314625

UCB MANUFACTURING, INC.

331 CLAY RD

ROCHESTER, NY 146233226

DMF No: AADA:

Responsibilities:

- FINISHED DOSAGE LABELER
- FINISHED DOSAGE PACKAGER
- FINISHED DOSAGE RELEASE TESTER
- FINISHED DOSAGE STABILITY TESTER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : TTR OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-JAN-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

---

Establishment : CFN : FEI : [redacted]

[redacted]

b(4)

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-JAN-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
---
David Claffey
9/9/2008 02:29:13 PM
CHEMIST

Martha Heimann
9/9/2008 02:46:10 PM
CHEMIST
Signed for Ramesh Sood.

# NDA 22-285

## Keppra XR
## levetiracetam extended-release tablets

**UCB, Inc**

**David J. Claffey, PhD**

**ONDQA**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 22-285

2. REVIEW #1

3. REVIEW DATE: 14 MAY 2008

4. REVIEWER: David J. Claffey, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Information Request | 28 JAN 2008 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | 13 NOV 2007 |
| Amendment | 15 FEB 2008 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | UCB, INC. |
| Address: | 1950 Lake Park Drive, Smyrna, GA 30080 |
| Representative: | Cassie Buckhalt |
| Telephone: | 770 970 8621 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Keppra XR
b) Non-Proprietary Name (USAN): levetiracetam extended release tablets
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 501 (b) (1)

10. PHARMACOL. CATEGORY: Adjunctive Therapy in the Treatment of Partial Onset Seizures in Adults and Adolescents [redacted] years and older with Epilepsy. b(4)

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 500 mg

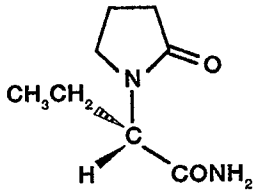
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(S)-(-)-alpha-ethyl-2-oxo-1-pyrrolidine acetamide
$C_8H_{14}N_2O_2$
MW = 170.21




## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
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b(4)

[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 | 76,812 | IND for Keppra XR |
| NDA | 21-035 | Keppra Tablets (cross referenced for drug substance information) |
| NDA | 21-505 | Keppra Oral Solution |
| NDA | 21-872 | Keppra Injection |

## 18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| EES | Not complete | | |
| Pharm/Tox | Not complete | | |
| Biopharm | Not complete | | Ta-Chen Wu, PhD |
| EA | FONSI | 25 FEB 2008 | Raanan A. Bloom, PhD |

## 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 22-285

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

This Application is approvable from a CMC perspective pending an acceptable response to the information request sent to the Applicant on 21 May 2008 and the overall recommendation from the Office of Compliance.

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

## II. Summary of Chemistry Assessments

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

The drug product will be supplied for oral administration as a single strength (500 mg) oblong, white film-coated extended-release tablets with red imprinting in bottles [redacted]. The tablet [redacted] is composed of [redacted] hypromellose. [redacted] is comprised of silica, PEG and [redacted]

b(4)

[redacted] and is currently approved for use in similar quantities in the cross-referenced immediate release tablet. It has no effect on the drug release properties.

The drug substance is highly water soluble (1 g/ml) with no known polymorphs. The currently marketed immediate-release dosage form has near 100% bioavailability. Development aimed at producing an equivalent extended-release formulation in a reasonably-sized tablet. Three different slow release formulations (F1, F2 and F3) were selected for PK study versus an immediate-release tablet in Study N01140. Subsequent Phase 3 clinical studies used another formulation, F4, which is identical to the proposed commercial formulation with the exception of [redacted]

b(4)

The film-coated tablets are manufactured and packaged by UCB Pharma in Brain-L'Alleud, Belgium and the imprinting is carried out at the UCB Farchim SA site in Bulle Switzerland. CDER OC has not yet issued an overall recommendation regarding these sites. An information request has been sent to the Applicant concerning several aspects of the manufacturing process including control of the hypromellose, blend uniformity and tablet hardness. The drug product dissolution method is adequate and was demonstrated to be discriminatory over a range of hypromellose concentrations.

Data up to 12 months at 25°C/60%RH and 6 months at 40°C/75%RH for the three of the four primary stability lots was provided. These three lots have the same formulation as the commercial lots but contain [redacted] The forth primary stability lot is identical in formulation to the commercial lots [redacted]. Three months data is available for this lot at both accelerated and long-term storage conditions. Some supportive stability data (six months) was also provided for the [redacted] tablets which were used during development. All these lots were manufactured at pilot-scale at the proposed commercial manufacturing site and were packaged in both commercial packaging presentations. All results remained within specified limits and no significant changes were noted thus-far. The Applicant will be asked to provide updated stability data to provide further assurance of the proposed 24 month expiry period at 25°C/60%RH. b(4)

The drug substance, levetiracetam, is a water soluble single (S-) enantiomer. It is known to be stable in slightly acidic aqueous media, such as that proposed in the drug product dissolution test. All CMC information regarding levetiracetam is cross referenced to the approved NDA 21-035 (Keppra Tablets). The release specifications for levetiracetam are equivalent to those in the cross referenced application. The retest date for levetiracetam is [redacted], based on ICH stability data provided to the cross referenced application. b(4)

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

This application proposes the use of KEPPRA XR™ as adjunctive therapy in the treatment of partial onset seizures in patients [redacted] years of age with epilepsy.

It is proposed that treatment 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. There is no evidence that doses greater than 3000 mg/day confer additional benefit.

### C. Basis for Approvability or Not-Approval Recommendation

At this time this application is approvable. An approval recommendation will depend on the response to the 21 May 2008 information request and the overall recommendation from the Office of Compliance.

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

DClaffey: Same date as draft review

MHeimann
RSood
SDaugherty

**C. CC Block**

# 44 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Chemistry-* 3

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/s/
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David Claffey
5/23/2008 11:39:07 AM
CHEMIST

this is the revised copy

Ramesh Sood
5/23/2008 11:43:08 AM
CHEMIST

# Initial Quality Assessment
# Branch I
# Pre-Marketing Assessment Division I

| | |
|---|---|
| **OND Division:** | Division of Neurology Products |
| **NDA:** | 22-285 |
| **Applicant:** | UCB Pharma |
| **Stamp Date:** | 14-Nov-2007 |
| **PDUFA Date:** | 14-Sep-2008 |
| **Trademark:** | KEPPRA XR® |
| **Established Name:** | Levetiracetam |
| **Dosage Form:** | Extended release tablets |
| **Route of Administration:** | Oral |
| **Indication:** | Epilepsy |
| **PAL:** | Martha R. Heimann, Ph.D. |

| | Yes | No |
|---|---|---|
| **ONDQA Fileability:** | ☒ | ☐ |
| **Comments for 74-Day Letter** | ☒ | ☐ |

## Summary and Critical Issues:

### *Summary*

Levetiracetam (chemical name: (S)-(-)-α-2-oxo-1-pyrrolidine acetamide) is currently approved for use as adjunctive therapy in the treatment of partial onset seizures, treatment of myoclonic seizures, and treatment of primary generalized tonic-clonic seizures. Currently, three dosage forms are available, i.e., conventional immediate release tablets (250 mg, 500 mg, 750 mg and 1000 mg), oral solution (100 mg/mL), and injection (100 mg/mL). The current NDA provides for a 500 mg levetiracetam extended-release tablet formulation for adjunctive treatment of partial onset seizures in patients [redacted] years of age or older. The extended release formulation would allow for a reduction in dosing frequency to once daily. b(4)

*Drug Substance*

The active ingredient, levetiracetam, is a well characterized small molecule with molecular formula $C_8H_{14}N_2O_2$ and molecular weight 170.21. The drug substance is highly soluble in water (~1.04 g/mL at 25°C). Levetiracetam does not exhibit polymorphism. The applicant cross-references approved NDA 21-035 (Keppra Tablets) for all CMC information related to the bulk drug substance.

*Drug Product*

Keppra XR Tablets are extended release, oblong, white film-coated tablets containing 500 mg of levetiracetam. [redacted]
The quantitative composition for the proposed commercial tablets is presented below. The product will be packaged for commercial distribution in [redacted] HDPE b(4)

bottles [redacted] b(4)

Table 3:1 Proposed Composition for Levetiracetam Extended Release Tablets, 500 mg

| Ingredient | Amount per Tablet (mg) | Function | Reference to Standard |
|---|---|---|---|
| Levetiracetam | 500.00 | Active ingredient | UCB Specification |
| Hypromellose | [redacted] | | Ph. Eur. |
| Colloidal anhydrous silica | | | Ph. Eur. |
| Polyethylene glycol | | | Ph. Eur. |
| Magnesium Stearate | | | Ph. Eur. |
| [redacted] | | | |

b(4)

All ingredients except the [redacted] film-coat and imprinting ink formulations are compendial. Per prior agreement, the firm will test compendial excipients using European Pharmacopeia test procedures, with a commitment to perform periodic testing to verify compliance with official USP/NF requirement. [Refer to pre-IND meeting for IND 73,703, 19-Apr-2006. This was also approved for Keppra Tablets under NDA 21-035/S-048.] b(4)

The proposed commercial tablet formulation is the same formulation used in all pivotal studies in support of the NDA except for the [redacted] The applicant has submitted the results from a multimedia comparative drug release study to support the equivalency of [redacted] tablets. b(4)

Keppra XR Tablets will be manufactured by UCB at the firm's facility in Braine-l'Alleud, Belgium. The manufacturing process involves conventional manufacturing techniques, i.e., [redacted] b(4)

The proposed regulatory specifications for Keppra XR Tablets involve straight-forward analytical procedures. Assay and achiral impurities are determined using [redacted] Drug release is determined using USP Apparatus I at 100 rpm with 900 mL pH 6.0 phosphate buffer as the dissolution medium. Tablet dissolution results are quantitated by HPLC, however, the method is different from that used for assay and related substances. Although methods validation data are provided for all analytical procedures; it is noted that no information was provided to support the choice of dissolution parameters for this product. b(4)

The NDA primary stability package includes 12 months of long-term data, plus 6 months accelerated data for 3 batches of white, film-coated [redacted] 500 mg tablets (clinical image) and 3 months of long-term/accelerated data for one batch of market image, white, film-coated, [redacted] tablets. Supportive stability data through 6 months (long-term and accelerated) are provided for one batch of [redacted] 500 mg tablets. The [redacted] tablets were originally intended to be the commercial image. During the pre-IND meeting for IND b(4)

73,703, the Agency agreed to accept the data from the white, [redacted] tablets, plus 6 months data for one batch [redacted] tablets as primary stability data. The minor change from [redacted] tablets is not likely to impact on product stability. b(4)

## Critical issues for review

*Drug Substance*

No critical issues are identified. Given the high solubility of the drug substance (~ 1 g/mL) and the [redacted], it is unlikely that physical properties of the drug substance would impact on tablet properties (e.g., drug release) or on manufacturability (e.g., content uniformity). b(4)

*Drug Product*

The drug product is a relatively simple, eroding matrix type, extended-release tablet manufactured using conventional manufacturing processes. No critical issues were identified during the initial assessment; however the following points are noted:

- The pharmaceutical development section provides a very brief discussion of the development history for this extended-release formulation. Almost no data are provided by the applicant to support the choices of excipients, final formulation, manufacturing process or critical process parameters. It is also noted that the clinical development program was short and involved relatively few tablet batches. Thus, there is limited manufacturing experience to support the robustness of either the commercial formulation, or the commercial manufacturing process.

- No information is provided to support the appropriateness of proposed dissolution method. Thus the adequacy of the method for quality control purposes cannot be fully evaluated.

## Additional issues

*Administrative:* An updated environmental assessment for levetiracetam is included in the initial submission. [File location: cmc\environ.pdf] It is requested that the ONDQA Project Manager arrange for a consult review.

*Establishment Evaluation:* Manufacturing sites for the drug product are identified on the Form 356h. Drug substance manufacturing sites are identified within the submission; however, they are not listed on the 356h and the information in the submission is not complete. It is requested that the ONDQA Project Manager contact the applicant to obtain site contact information, including U.S. agents as appropriate, and registration numbers for the facilities listed in Attachment 1 prior to entry into EES. Additionally, the applicant should confirm that all manufacturing facilities for drug substance and drug product are ready for inspection.

*Labeling/Established Name*: The active ingredient, levetiracetam, is a neutral molecule with no ionizable functional groups. There are no issues related to consistency between the established name and labeled potency.

## *Comments for 74-Day Letter*

With regard to the proposed specification for Keppra XR Tablets, you have not provided any data to support the suitability of the proposed dissolution/drug release method. The following information is needed to assess the adequacy of the method for quality control purposes

- Provide a rationale, and supporting data as appropriate for the choice of dissolution apparatus, rotation speed, and dissolution media.
- Provide data to demonstrate the ability of the method to discriminate between acceptable and unacceptable batches.

Container closure documentation for [redacted] HDPE bottles is provided in the application. Clarify whether the [redacted] will be used for commercial distribution or professional samples and provide the appropriate container labels for review. b(4)

## Review, Comments and Recommendation:

*Fileability:* The application is fileable; however, there are some minor issues related to the completeness and reviewability of the application that should be addressed with the applicant prior to filing.

- The application is submitted electronically in a "hybrid" format, i.e., technical sections follow CTD format, but the administrative portions, including labeling, do not. The main Table of Contents (ndatoc.pdf) is incomplete and does not provide links to some required elements. As an example, the ndatoc.pdf file does not contain a link to the environmental assessment. The link to the environmental assessment is contained in a separate file titled "ctdmap.pdf". Certain hyperlinks from the Main TOC to other section TOCs are inoperable, as are the links CMC subsections back to the Main TOC. The OND project manager has advised the firm that there is an issue with hyperlink functionality.
- The applicant has not submitted the required methods validation package. This may be an oversight as the submission contains links to the methods validation section. The actual file "methval.pdf" is not present in the electronic submission. The applicant will be asked to submit this information.

*Review:* It is recommended that a single reviewer be assigned to the NDA. No novel manufacturing processes are involved; this, the submission does not appear to require review by the Manufacturing Sciences Branch.

Martha R. Heimann, Ph.D. — 12/3/07
Pharmaceutical Assessment Lead — Date

Ramesh Sood, Ph.D. — 12/3/07
Branch Chief — Date

# ATTACHMENT 1

## Manufacturing Sites for Keppra XR Tablets

| Facility Information | Function |
|---|---|
| UCB Pharma S.A.<br>Site de Braine-l'Alleud, Bldg. 2<br>Chemin du Foriest<br>1420 Braine-l'Alleud<br>Belgium<br><br>Registration No.: 3002808410<br>Site Contact: [redacted]<br>Tel. No.: +32 (2) 386-3401<br><br>US Agent:<br>Phone: | Drug substance manufacturer, release and stability tester<br>Drug product manufacturer, packager, release and stability tester |
| [redacted] | |
| UCB Farchim SA<br>Zone Industrielle de Planchy<br>Chemin de Croix Blanche, 10<br>Bulle 1630<br>Switzerland<br><br>Registration No.: 3005023799<br>Site Contact: [redacted]<br>Tel. No.: +41 (26) 9190-224<br><br>US Agent:<br>Phone: | Drug substance manufacturer, release and stability tester<br>Drug product manufacturer, imprinting operations only |
| [redacted] | |

b(4)

b(4)

b(4)

b(4)

# ATTACHMENT 1

## Manufacturing Sites for Keppra XR Tablets

| Facility Information | Function |
|---|---|
| UCB Manufacturing, Inc.<br>331 Clay Road<br>Rochester, NY 14623<br><br>Registration No.: 1314625<br>Site Contact: [redacted]<br>Tel. No.: 585 274-5343 | Drug product packaging [redacted] |

b(4)

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

**NDA Numbers:** [redacted] **Applicant:** [redacted] **Stamp Date: 28-Sep-2007** b(4)

**Drug Name:** [redacted] **NDA Type: Standard** **Filing Meeting: 20-Nov-2007**

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 | | Some hyperlinks invalid. |
| 2 | Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)? | | X | 11/27/07—contact information and CFN needed for one D.S. facility. US agent information needed for foreign sites |
| 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 | | 11/27/07 Not found |
| 4 | Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)? | X | | |
| 5 | Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)? | X | | Cross reference to NDA 21-035 |
| 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? | X | | |
| 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? | X | | |
| 11 | Is information on the Methods Validation included? | | X | File 'methval.pdf' is referenced in submission, but not found. |
| 12 | If applicable, is documentation on the sterilization process validation included? | NA | | |

**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.

Martha R. Heimann, Ph.D. 12/3/07

Pharmaceutical Assessment Lead, DPA 1, ONDQA Date

Ramesh Sood, Ph.D. 12/3/07

Branch Chief, DPA 1, ONDQA Date

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
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Martha Heimann
12/3/2007 02:56:06 PM
CHEMIST

Ramesh Sood
12/4/2007 09:33:52 AM
CHEMIST