

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-505

ENVIRONMENTAL ASSESSMENT

**REVIEW OF
ENVIRONMENTAL ASSESSMENT**

For •

KEPPRA ORAL SOLUTION

(100 mg/mL Levetiracetam)

NDA 21-505

**Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
(HFD-120)**

Date Completed: October 31, 2002

EXECUTIVE SUMMARY – ENVIRONMENTAL ASSESSMENT**FONSI recommended**

Recommendation is based on original EA dated August 14, 2001 and responses in amendment dated October 23, 2002 to comments conveyed by telephone by FDA / Thomas Broadbent.

- (1) Pages 1085 to 1099 of the Environmental Assessment dated August 14, 2001 may be released to the public.
- (2) The solubility of the drug substance (levetiracetam) reported in Appendix A (Chemical Data Summary) is 1040 grams per liter of water.
- (3) The logs of the octanol/water partition coefficients are reported in Appendix A (Chemical Data Summary).
- (4) The typographical errors in Section 5 iii (Identification of Substances....) were corrected by UCB Pharma.

Levetiracetam (drug substance) and its acid metabolite are excreted in the urine. Therefore, effect data were generated for the aquatic environment.

Neither compound is volatile (Vapor pressure $< 6 \times 10^{-5}$ torr). They will not enter the air compartment. The high aqueous solubility of levetiracetam (drug substance) and its acid metabolite indicates adsorption to sludge is unlikely.

Levetiracetam (drug substance) and its acid metabolite will enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). The Expected Introduction Concentration (EIC_{aquatic}) is 2.89 ppb assuming no metabolism, no hydrolysis, no adsorption to sludge and no photolysis. This EIC is based on the prediction of the total amount of drug substance manufactured for levetiracetam tablets and oral solution sold in the USA in 2006.

The Expected Environmental Concentration (EEC) in the aquatic environment is less than calculated using a dilution factor of 10 for wastewater effluents discharged into the receiving waters. Slow hydrolysis is the expected depletion mechanism for levetiracetam in the aquatic environment.

It is unlikely that levetiracetam and its acid metabolite represent a risk to the aquatic environment based on the available environmental effect data.

Environmental Effect Data for levetiracetam (active drug) in EA dated Aug 14, 2001

Activated sludge inhibition	EC ₅₀ greater than 1000 mg/L	NOEC ≥ 1000 mg/L
Daphnia magna, acute	48 hour EC ₅₀ > 100 mg/L	NOEC ≥ 100 mg/L

REVIEW #1 of ENVIRONMENTAL ASSESSMENT

Project Manager: Melina Fanari, 4-5526 Chemist: Tom Broadbent, 4-5507

1. **Date:** EA dated August 14, 2001
Amendment dated Oct 23, 2002
2. **Name of applicant/petitioner:** UCB Pharma Inc.
3. **Address:** 1950 Lake Park Drive, Smyrna, Georgia 30080
4. **Description of the proposed action:**

a. Requested Approval:

This NDA 21-505 requests approval to market Keppra Oral Solution (100 mg levetiracetam per mL), an anti-epileptic for adjunct therapy in the treatment of partial onset seizures, in adults with epilepsy.

ADEQUATE

b. Need for Action:

NDA 21-505 requests approval of Keppra Oral Solution (100 mg levetiracetam/mL).

UCB Pharma filed NDA 21-505 pursuant to section 505(b) of the Federal, Food, Drug and Cosmetic Act for Keppra Oral Solution (100 mg levetiracetam per mL), an anti-epileptic for adjunct therapy in the treatment of partial onset seizures, in adults with epilepsy.

The associated EA was submitted pursuant to 21 CFR 25.31a (a), following the Center for Drug Evaluation and Research "Guidance for Industry for the Submission of an Environmental Assessment" dated July 1998.

A FONSI was not prepared for NDA 21-035 for Keppra Tablets (250 mg, 500 mg and 750 mg levetiracetam) that was approved on Nov 30, 1999.

ADEQUATE

c. Expected Locations of Use (Drug Product):

Keppra Oral Solution will be used in hospitals, clinics and in the patient's home. It will be used throughout the U.S.

ADEQUATE

d. Disposal Sites

Empty or partially empty packages containing Keppra Oral Solution will be disposed by a community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of unused drug may be disposed in the sewer system.

ADEQUATE

5. Identification of chemicals that are the subject of the proposed action:**Nomenclature (levetiracetam)**

- i. Established Name (USAN): levetiracetam (a.k.a. ucb L059)
- ii. Trade Name: Keppra Oral Solution
- iii. Chem Abstracts: 1-pyrrolidine acetamide, α -ethyl-2-oxo-, $[\alpha S]$ -
- iv. Systemic Name: (-)-(S)- α -ethyl-2-oxo-1- pyrrolidine acetamide
- v. CAS Number: 102767-28-2

Molecular Formula: $C_8H_{14}N_2O_2$

Molecular Weight: 170.21

Chemical Structure is in the EA, Section 4, Volume 11, page 1091

ADEQUATE

6. Environmental Issue:

The active drug substance is manufactured and packaged in the EU and USA. Keppra Oral Solution is manufactured and packaged in the USA. The total quantity of active drug substance required for all Keppra products (tablets and oral solution) for the USA market in 2006 is projected to be 128 metric tons. The resultant EIC aquatic is 2.89 ppb.

ADEQUATE

a. Environmental Fate of Released Substances

i. Identification of Substances of Interest

95% of the administered dose is excreted in the urine.
66% is excreted unchanged, namely as ucb L059.
24% is excreted as an acetic acid metabolite, ucb L057.

The major metabolic pathway is enzymatic hydrolysis of the acetamide group. The acid metabolite, ucb L057, has no known pharmacological activity.

Both substances, ucb L057 and ucb L059, are readily soluble in water. As a result, they will be in the aquatic environment.

If all the active drug substance (ucb L059) were introduced into the aquatic environment unchanged, The EIC would be 2.89 ppb.

If human metabolism is considered, the EIC for ucb L059 is reduced to 1.91 ppb, namely 66% of 2.89 ppb.

The EIC for ucb L057 is 0.69 ppb, namely 24% of 2.89 ppb.

Environmental fate data were obtained for the active drug substance and the metabolite.

Environmental effects testing was performed for ucb L059 only.

- (a) Inhibition of Respiration of Activated Sludge
- (b) Ready Biodegradability by Measurement of CO₂ Evolution
- (c) Acute toxicity to *Daphnia magna* (48-hour Immobilization)

ADEQUATE

ii. Physical and Chemical Characterization

Physical and Chemical characteristics of ucb L059 and ucb L057 are summarized in Appendix A, page 1099 and a Final Report (UV spectrum and hydrolysis rate) in Section. 4.9.71, p 1133.

Test	Drug Substance	Metabolite
Solubility, g/L of H ₂ O @ 25°C	1,040	195.20
Dissociation constant, pKa	Less than -2	3.67 ± 0.02
Log Octanol/water partition coeff.	-0.64 ± 0.02 @ 25°C	0.82 @ 25°C
Vapor pressure, mm Hg	1.27 x 10 ⁻⁵	5.85 x 10 ⁻⁵
Hydrolysis (OECD # 111)	Stable @ pH 4 to 9 @ 50.8°C	Stable @ pH 5 to 9 @ 25°C
UV/VIS absorption spectrum	Very weak from 200 to 800 nm	

EVALUATION, Assessment of Studies: The data appear to be generated using standard and acceptable scientific methods.

ADEQUATE

iii. Environmental Depletion Mechanisms

Abiotic hydrolysis of the drug substance, ucb L059, was evaluated according to a GLP protocol (page 1128). The final report is in an Appendix to the EA (pages 1126 to 1171). Not more than 10% of the drug substance hydrolyzes in 5 days at environmental pH. The drug substance is stable.

Hydrolysis at 50.8°C (% Loss of ucb L059 in 5 days)	
Citric acid @ pH 4	1.0 %
Phosphate buffer @ pH 7	1.5 %
Borate buffer @ pH 9	3.6 %

Ready Biodegradability by Measurement of Carbon Dioxide Evolution was assessed according to the OECD Guideline 301 (page 1183). GLP protocol was followed (page 1177). The final report is in an Appendix to the EA (pages 1172 to 1201). Not more than 4% degradation was observed in 28 days. Therefore, ucb L059 is not readily biodegradable.

This test does not simulate a real aquatic environment. The test is only used to identify substances that degrade rapidly and completely in natural water bodies. A substance classified as “not readily biodegradable” may be fully biodegradable.

ADEQUATE

iv. Environmental Concentration, aquatic, levetiracetam

The total amount of levetiracetam drug substance needed in the USA for all drug products described in NDA 21-035 (tablets) and NDA 21-505 (oral solution) is estimated to be 128,000 kg in 2006. (Reference: Confidential Appendix C, Volume 11, page 1101) The Expected Introduction Concentration (EIC_{aquatic}) of levetiracetam into the external aquatic environment is 2.89 ppb (≈ 0.003 mg/L). This assumes no metabolism and no removal on solids in the POTW. This is the concentration used in the risk assessment for effects on microorganisms and acute toxicity studies.

ADEQUATE

Summary Environmental Fate of Released Substances

Levetiracetam (drug substance) and “ucb L 057” (major acid metabolite) are not volatile and therefore will not enter the air compartment.

The high aqueous solubility of levetiracetam and its metabolite and their small octanol / water partition coefficients indicate that adsorption to sewage sludge is unlikely.

Levetiracetam and its metabolite will enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). The Expected Introduction Concentration (EIC_{aquatic}) for levetiracetam is 2.89 ppb assuming 128,000 kg per year, no hydrolysis, no metabolism, no adsorption to sludge and no photolysis.

ADEQUATE

b. Acute Environmental Effect of Levetiracetam (drug substance)

Adverse environmental effects resulting from the clinical use of Keppra Tablets and Oral Solution are not expected at the predicted production levels. This was assessed by comparing the EIC (2.89 ppb) with experimental ecotoxicity data for levetiracetam (drug substance) obtained by using scientifically sound methods (OECD Protocols) in conformance with GLP principles.

i. Acute Toxicity to *Daphnia Magna*, 48-hour Immobilization

The EC₅₀ value for *Daphnia magna* Immobilization (48-hour acute toxicity test) is > 100 mg/L. The EC₅₀ / EIC ratio is greater than 34,000. This ratio is greater than the minimum Tier 1 requirement (1000)

NOEC is ≥ 100 mg/mL. NOEC is much greater than EIC.

ADEQUATE

ii. Inhibition of Respiration of Activated Sludge (OECD 209)

No inhibition was observed at 3 hours at concentrations of levetiracetam from 1 mg/mL up to and including 1000 mg/L, the highest concentration tested.

NOEC is ≥ 1000 mg/mL. NOEC is much greater than EIC.

ADEQUATE

Summary of Environmental Effects Data

Acute toxicity testing in *Daphnia magna* shows that the EC₅₀ to EIC (expected introduction concentration) ratio is greater than 1000. Toxic effects were not observed. (NOEC ≥ 100 mg/L)

Levetiracetam did not inhibit respiration of activated sludge at concentrations up to and including 1000 mg/mL. NOEC is ≥ 1000 mg/mL.

The introduction of levetiracetam into the environment through use and disposal of the product is not expected to pose an environmental risk. Based on the information available to date, a FONSI will be recommended after the applicant responds to comments in the Draft Letter.

7. Mitigation Measures

No adverse environmental effects have been identified.
No mitigation measures are required.

ADEQUATE

8. Alternatives to the proposed action

No potential effects have been identified for this proposed action.
No alternatives to the proposed action are required.

ADEQUATE

9. Preparer

Name and professional experience is provided in the EA, Section 4, Vol. 11,
pages 1095-6 and 1102

ADEQUATE

10. References

References are provided in the EA, page 1097

ADEQUATE

11. Appendices

The EA contains a Data Summary Table (page 1099)

The EA contains a confidential calculation of the Expected Introduction Concentration (EIC) for Levetiracetam (drug substance) and “ucb L 057” (major acid metabolite).

The EIC for levetiracetam is based on the projected annual maximum amount of drug substance needed in the USA to support all drug products and dosage forms manufactured by Ucb Pharma, Inc in 2006. (Confidential Appendix C, page 1101).

The EIC for ucb L 057 is based on metabolism of drug substance. (See EA pages 1091 to 1095).

The Appendix to the EA contains 4 reports:

- i. Determination of Inhibition of Respiration of Activated Sludge
- ii. Determination of Physico-Chemical Properties (UV Spectroscopy and Hydrolysis Rate)
- iii. Assessment of Ready Biodegradability by Measurement of Carbon Dioxide Evolution
- iv. Acute toxicity to Daphnia Magna in a 48-hour Immobilization Test.

ADEQUATE

Florian Zielinski
October 31, 2002

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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10/31/02 03:15:02 PM
ENV ASSESSMENT

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10/31/02 03:51:11 PM
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11/1/02 04:45:58 PM
CHEMIST
concurred

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
for
KEPPRA ORAL SOLUTION
(100 mg/mL Levetiracetam)

NDA 21-505

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
(HFD-120)

October 31, 2002

FINDING OF NO SIGNIFICANT IMPACT

NDA 21-505

KEPPRA ORAL SOLUTION (100 mg/mL levetiracetam)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of its supplemental new drug application for Keppra Oral Solution, UCB Pharma Inc. has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal of the product.

Levetiracetam is a chemically synthesized drug that is currently approved for adjunct therapy of partial onset seizures in adults with epilepsy. This application provides for the use of Keppra Oral Solution (100 mg/mL levetiracetam) for adjunct therapy of partial onset seizures, with or without secondary generalization, in adults with epilepsy.

Levetiracetam may enter the environment from patient use and disposal. It is expected to enter predominately into the aquatic environment. As the drug is expected to persist in the environment for some time, the toxicity of Levetiracetam to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at expected environmental concentrations.

In U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of the unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

**Keppra™ (levetiracetam) :
Environmental Assessment**

Data Requirement

US Department of Health and Human Services, Food and Drug Administration,
Center for Drug Evaluation and Research (CDER)/Center for Biologics Evaluation
and Research (CBER): Environmental Assessment of Human Drug and Biologics
Applications, July 1998, CMC 6, Revision 1.

Covance Reference Number 1047/085
UCB Report Reference Code RXLE02D2903

Conducted by: Eamonn Farrelly, E F Consulting Ltd
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Chemin du Foriest, B-1420 Braine-l'Alleud
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10th May 2002

Covance Reference No. 1047/065 Keppra™ (levetiracetam): Environmental Assessment
UCB Report Reference Code: KXLEUZD2903

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EXECUTIVE SUMMARY

The anti-epileptic agent, Keppra™ (known as ucb L059 and Levetiracetam), has been approved by US FDA for adjunct therapy in the treatment of partial onset seizures in adults with epilepsy. The product is available as Keppra™ Tablets (250 mg, 500 mg and 750 mg levetiracetam) with a recommended dose of 1000 to 3000 mg/day. It is expected to become available as Keppra™ Oral Solution (100 mg/ml levetiracetam) with a recommended dose of 1000 to 3000 mg/day. Approximately 2.5 million people in the U.S. suffer from epilepsy. Keppra™ will be used by patients in hospitals, clinics and/or by outpatients. Given the nature of the disease, Keppra™ is expected to have wide geographical usage throughout the U.S.

Metabolism studies in humans indicate that 95% of the administered dose is excreted in the urine, 66% as ucb L059 and 24% as the major acid metabolite, ucb L057. The aquatic environment is therefore considered the compartment of potential concern with the principal exposure route via Publicly Owned Treatment Works (POTWs).

The EIC-aquatic for ucb L059 is above 1 part per billion (ppb or µg/L) and thus further environmental assessment using the tiered approach is necessary. Laboratory studies have demonstrated that ucb L059 is hydrolytically stable at environmentally relevant pHs and cannot be considered readily biodegradable. However there was no suppression of biodegradation processes in the presence of ucb L059 and no inhibition of the aerobic respiratory processes in activated sewage sludge at concentrations of ucb L059 up to and including 1000 mg/L. Therefore the use of ucb L059 will not impact the microbial degradation processes in POTWs.

Following acute toxicity testing with *Daphnia magna* (EC_{50} 48 h > 100 mg/L), the Tier 1 assessment factor for ucb L059 is well in excess of the 1000 trigger value. In addition the low octanol:water partition co-efficient for ucb L059 means that it is unlikely to concentrate in biosolids (sewage sludge) or aquatic sediments and its potential to bioaccumulate or bioconcentrate in the environment would be negligible.

Covance Reference No. 1047085

Keppra™ (levetiracetam): Environmental Assessment
UCB Report Reference Code: RXLE02D2903

No adverse environmental effects have been identified nor are anticipated from the expected entry of ucb L059 into the environment.

The major metabolite, ucb L057, is a polar acid metabolite with no known pharmacological activity. Its potential to bioaccumulate or bioconcentrate in the environment is low and the EIC-aquatic is below 1 part per billion (ppb or µg/L). Therefore, under U.S. FDA guidance, further assessment of environmental impact is not required.

No adverse environmental effects have been identified nor are anticipated from the proposed use of Keppra™.

Covance Reference No. 1047085

Keppra™ (levetiracetam): Environmental Assessment
UCB Report Reference Code: RXLE02D2903

1. **DATE**

14th August 2001

2. **NAME OF APPLICANT/PETITIONER**

UCB Pharma, Inc.

3. **ADDRESS**

UCB Pharma, Inc.
1950 Lake Park Drive
Smyrna
Georgia 30080
USA

4. **DESCRIPTION OF PROPOSED ACTION**

a. **Requested Approval**

UCB Pharma Inc., 1950 Lake Park Drive, Smyrna, Georgia 30080, USA has filed a New Drug Application (NDA) pursuant to section 505 (b) of the Federal Food, Drug and Cosmetic Act for Keppra™ Oral Solution (100 mg/ml levetiracetam) with a recommended dose of 1000 to 3000 mg/day. The oral solution is packaged in 2 oz glass, 16 oz glass, 2 oz HDPE and 16 oz HDPE bottles. This medicine is available only with a doctor's prescription. An Environmental Assessment (EA) has been submitted pursuant to 21 CFR Part 25.

Levetiracetam is also the active ingredient described in the approved UCB Pharma Inc. NDA #21-035 (30 November 1999). Keppra™ tablets (250 mg, 500 mg and 750 mg levetiracetam) are packaged in the form of blisters or HDPE bottles with a recommended dose of 1000 to 3000 mg/day.

b. **Need for Action**

The anti-epileptic agent, ucb L059 - a pyrrolidone derivative, is intended for adjunct therapy in the treatment of partial onset seizures, with or without

secondary generalization, in adults with epilepsy. Partial seizures, which are the most common type of seizures in adults, may be characterized by impaired consciousness, loss of awareness, involuntary motor behaviours, and other non-conscious, involuntary events. For physicians and patients, the attraction of Keppra™ is that it increases seizure control without adverse interaction with co-administered anti-epileptic drugs. Approximately 2.5 million people in the U.S. suffer from epilepsy.

c. Locations of Use

Keppra™ is available only with a doctor's prescription and will be used in hospitals, clinics and/or by patients in their homes. Given the nature of the disorder, the medicine is expected to have wide geographical usage throughout the U.S.

d. Disposal sites

The principal disposal routes at hospitals, pharmacies and clinics throughout the U.S. will be according to recognised local procedures for clinical waste. Disposal after home use will be typically unused or partially empty containers disposed via solid waste management systems, including landfills, incineration and recycling of packaging materials. It is expected that minimal quantities of unused drug will be disposed of in sewage systems.

5. IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

a. Chemical Nomenclature

- | | | |
|------|--------------------------|---|
| i. | Established Name (USAN) | ucb L059 (Levetiracetam) |
| ii. | Trade name | Keppra™ |
| iii. | Chemical Abstracts Name | 1-Pyrrolidine acetamide, α -ethyl-2-oxo-,
[α S]-; |
| | Systematic Chemical Name | (-)-(S)- α -ethyl-2-oxo-1-pyrrolidine
acetamide |

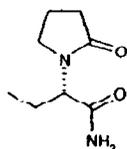
b. Chemical Abstracts Service (CAS) Number

102767-28-2

Covance Reference No. 1047085

Keppra™ (levetiracetam): Environmental Assessment
UCB Report Reference Code: RXLE02D2903

- c. **Molecular Formula**
C₈H₁₄N₂O₂
- d. **Molecular Weight (g/mol)**
170.21
- e. **Structural Formula**



Stereochemistry: S-enantiomer

6. ENVIRONMENTAL ISSUES

The active substance, ucb L059 is manufactured and packaged in sites in the European Union (EU) and in the United States (US). The Keppra™ Oral Solution is manufactured and packaged in the United States, whilst the Keppra™ Tablets are manufactured in the EU and shipped in tablet form for subsequent packaging in the United States. These manufacturing sites are subject to both national and EU legislative controls on their operations and emissions. The marketed quantity of ucb L059 projected in 2006 for both the oral solution and the tablet is provided in Confidential Appendix C. It is expected to be 128 metric tonnes.

Pharmacokinetic and metabolism studies in humans indicate that, after a single oral administration of ucb L059, the compound is rapidly and almost completely absorbed (reference 1). Bioavailability is not affected by food. The pharmacokinetics are linear and time-invariant with low intra- and inter-subject variability. In total a mean of 95% of the administered dose is excreted in the urine. Sixty-six percent (66%) of the dose is renally excreted as parent compound (ucb L059), with the major acid metabolite, ucb L057 (Appendix A) constituting twenty-four percent (24%). The major metabolic pathway is enzymatic hydrolysis of the acetamide group. The acid metabolite, ucb L057, has no known pharmacological activity (reference 2).

The principal route of environmental exposure from product use in the U.S. will be following patient usage via Publicly Owned Treatment Works (POTWs). In addition given that both ucb L059 and ucb L057 have low vapour pressures and are readily soluble in water (Appendix A), the aquatic environment is considered the environmental compartment of potential concern.

The Expected Introduction Concentration (EIC) of the active moiety into the aquatic environment has been calculated according to guidance from the U.S. FDA (reference 3). This assumes that the total quantity of product shipped to the U.S. is used with an even geographical distribution throughout the U.S and at a constant daily rate. Given the widespread nature of the disorder in the human population, these assumptions are considered valid and appropriate.

$$\text{Total EIC - Aquatic (ppb)} = A \times B \times C \times D$$

where

$$\begin{aligned} A &= \text{kg/year as active moiety (Appendix C)} \\ B &= 1/1.214 \times 10^{11} \text{ litres per day entering POTWs (reference 4).} \\ C &= \text{year/365 days} \\ D &= 1 \times 10^9 \mu\text{g/kg (conversion factor)} \\ &= (128,000) \times (1/1.214 \times 10^{11}) \times (1/365) \times (1 \times 10^9) \\ &= 2.89 \mu\text{g/L (ppb)} \end{aligned}$$

Active moiety, ucb L059 in the aquatic environment

The EIC-aquatic for ucb L059 can be estimated by taking into account the metabolism of ucb L059 in humans (reference 1). The weighted contribution of ucb L059 within an EIC-aquatic can be calculated as follows

$$\text{ucb L059 EIC - Aquatic (ppb)} = A \times B \times C \times D$$

where

$$\begin{aligned} A &= \text{kg/year as active moiety (Appendix C) x 66% (reference 1)} \\ B &= 1/1.214 \times 10^{11} \text{ litres per day entering POTWs (reference 4).} \\ C &= \text{year/365 days} \\ D &= 1 \times 10^9 \mu\text{g/kg (conversion factor)} \\ &= (128,000 \times 66\%) \times (1/1.214 \times 10^{11}) \times (1/365) \times (1 \times 10^9) \\ &= 1.91 \mu\text{g/L (ppb)} \end{aligned}$$

The EIC-aquatic for ucb L059 is above 1 part per billion (ppb or $\mu\text{g/L}$) and thus a formal environmental assessment using the tiered approach in accordance with U.S. FDA guidance (reference 3) is necessary. The physico-chemical properties of both the active moiety and major metabolite have been determined (Appendix A).

The potential degradation of ucb L059 by both abiotic (hydrolysis) and biological (biodegradation) processes has been determined (references 5 and 6). The hydrolysis study demonstrated that ucb L059 is hydrolytically stable at environmentally relevant pHs. Furthermore ucb L059 did not undergo significant biodegradation and cannot be considered readily biodegradable. However the lack of significant mineralisation of ucb L059 under the stringent conditions in the study does not necessarily indicate that ucb L059 will not degrade in the natural environment.

The potential impact of ucb L059 on the microbial degradation processes in POTWs has been investigated. The absence of any suppression with respect to the degradation of a reference compound (sodium benzoate) in the presence of ucb L059, demonstrates that ucb L059 will not inhibit microbial degradation processes in POTWs (reference 6). In addition, there was no inhibition of the aerobic respiratory processes of the assorted micro-organisms present in activated sewage sludge at concentrations of ucb L059 up to and including 1000 mg/L (reference 7).

In accordance with the tiered approach, evaluation of the octanol/water partition coefficient (K_{ow}) indicates that Tier 1 acute toxicity testing is appropriate. The 48 hour EC_{50} value of ucb L059 to *Daphnia magna* was determined to be >100 mg/L (reference 8). Furthermore, no immobility of *D. magna* was observed in any of the test medium containing ucb L059.

The Tier 1 assessment factor (EC_{50} divided by the EIC-aquatic) for ucb L059 ($>100,000$ $\mu\text{g/L}/1.91$ $\mu\text{g/L}$) is well in excess of the 1000 trigger value. In addition, no sub-lethal effects were observed and therefore, under U.S. FDA guidance, further aquatic testing is not required. No adverse environmental effects have been identified from the expected entry of ucb L059 into the aquatic environment.

Covance Reference No. 1047/085

Keppra™ (levetiracetam): Environmental Assessment
UCB Report Reference Code: RXLE02D2903

The low octanol:water partition co-efficient for ucb L059 means that it is unlikely to concentrate in biosolids (sewage sludge) or aquatic sediments and its potential to bioaccumulate or bioconcentrate in the environment would be negligible.

Furthermore, the U.S FDA review of environmental assessment data (reference 9) indicates that in general, medical drugs are toxic to aquatic organisms at lower levels than they are to terrestrial organisms. Given the expected negligible exposure and absence of toxicity to *Daphnia* and to micro organisms in sewage sludge, ucb L059 is considered unlikely to pose a risk to the terrestrial environment.

No adverse environmental effects have been identified nor are anticipated from the expected entry of ucb L059 into the environment.

Acid metabolite, ucb L057 in the aquatic environment

The active moiety has one major acid metabolite, ucb L057, which has low vapour pressure, high water solubility and a low octanol:water partition co-efficient (Appendix A). Thus this polar molecule is unlikely to concentrate in biosolids or aquatic sediments and its potential to bioaccumulate or bioconcentrate in the environment would be negligible.

The EIC-aquatic for ucb L057 can be estimated by taking into account the metabolism of ucb L059 in humans (reference 1). The weighted contribution of the metabolite L057 within an EIC-aquatic can be calculated as follows

$$\text{ucb L057 EIC - Aquatic (ppb)} = A \times B \times C \times D$$

where

- A = kg/year as active moiety (Appendix C) x 24% (reference 1)
- B = 1/1.214 x 10¹¹ litres per day entering POTWs (reference 4).
- C = year/365 days
- D = 1 x 10⁹ µg/kg (conversion factor)

$$\begin{aligned} &= (128,000 \times 24\%) \times (1/1.214 \times 10^{11}) \times (1/365) \times (1 \times 10^9) \\ &= 0.69 \mu\text{g/L (ppb)} \end{aligned}$$

Covance Reference No. 1047085

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The EIC-aquatic for the acid metabolite ucb L057, is below 1 part per billion (ppb or µg/L) and thus below the criterion included in the FDA Environmental Assessment Final Rule of 29 July 1997 (reference 9).

In summary, the major metabolite, ucb L057, is a polar acidic metabolite with no known pharmacological activity. Its potential to bioaccumulate or bioconcentrate in the environment is low and the EIC-aquatic is below 1 part per billion (ppb or µg/L). Therefore, under U.S. FDA guidance, the conduct of further assessment is not required.

7. MITIGATION MEASURES

No adverse environmental effects have been identified nor are anticipated from the proposed use of Keppra™. Keppra™ is intended for use in adult patients with epilepsy and is available only with a doctor's prescription. The product packaging is specifically designed for individual treatment. The product has a limited and specific use, which will result in minimal exposure impact to the environment and therefore no mitigation measures are deemed necessary.

8. ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental effects have been identified for the proposed action, and therefore no reasonable alternative course of action that is environmentally preferable is deemed necessary.

9. LIST OF PREPARERS

Eamonn FARRELLY (MSc) – Environmental Specialist

E Farrelly is an independent environmental consultant with more than 20 years experience gained in environmental risk assessment primarily within the agrochemical industry. He is an experienced ecotoxicologist, specialising in freshwater aquatic effects testing and is also an experienced analytical chemist.

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Professional Qualifications:

Masters degree (M.Sc.) 1995 in Environmental Analysis and Assessment, Imperial College and Royal Holloway College, University of London.

Professional Memberships:

Society of Environmental Toxicology and Chemistry (SETAC) and United Kingdom Environmental Law Association (UKELA).

A curriculum vitae is included in Appendix D.

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10. REFERENCES

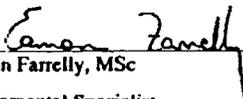
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Keppra™ (levetiracetam): Environmental Assessment
UCB Report Reference Code: RXLE02D2903

11. AUTHOR AUTHENTICATION

I, the undersigned, hereby declare that this report was compiled and prepared on behalf of Covance Laboratories Ltd.



Eamonn Farrelly, MSc
Environmental Specialist
E F Consulting Limited

10th May 2007
Date

12. APPENDICES

All of the data contained in the appendices B and C are considered confidential by the petitioner.

Covance Reference No. 1047/085

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Appendix A: CHEMICAL DATA SUMMARY

Physico-chemical property	ucb L059	Reference/test method	ucb L057	Reference/test method
Systematic chemical name	(-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide	Chemical Abstracts	(-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetic acid	Chemical Abstracts
Molecular weight (g/mol)	170.21	Mendeleiev Table	171.20	Mendeleiev Table
Water solubility (g/L at 25°C) ↑ of water	1040	Determination in saturated solution by densitometry and UV spectroscopy	195.20	Determination in saturated solution by HPLC
Dissociation constant (pKa)	< -2	Potentiometry and UV spectroscopy	3.67 ± 0.02	Potentiometry
Octanol/ water partition coefficient at 25°C	-0.64 ± 0.02	Micro shake flask technique	0.82	Micro shake flask technique
Vapour pressure (mm Hg)	1.27 x 10 ⁻⁵	Mackay method*	5.85 x 10 ⁻⁵	Mackay method*
Hydrolysis	Considered to be hydrolytically stable between pH 4 and 9 at 50.8 °C	OECD Guideline No.111	Considered to be hydrolytically stable between pH 5 and 9 at 25 °C	---

*FDAs/US
10/31/02*

Log

* Calculated using the Mackay method in the MP-BP-VP Computer Program, Syracuse Research Corporation, New-York 13210-4080, USA

Tier 1 Acute Toxicity Testing
Daphnia magna 48 hr EC50 > 100 mg/L
NOEC > 100 mg/L

No inhibition of aerobic respiration process in activated sewage sludge at 1000 mg L059 per liter

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/s/

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10/31/02 03:20:41 PM

Nancy Sager
10/31/02 03:55:27 PM

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Concurred