CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-253 & 22-254

ENVIRONMENTAL ASSESSMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: May 14, 2008

From: Raanan A. Bloom, Ph.D.
OPS/IO/PARS

To: Prafull Shiromani, Ph.D.
OPS/ONDQA/DPAI

Through: Jon Clark, M.S.
OPS/IO/PARS

Subject: **NDA 22-253**; Lacosamide Tablets: For the treatment of Epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older. Letter Date 9/28/07 b(4)
NDA —— Lacosamide Tablets: For the management of neuropathic pain associated with diabetic peripheral neuropathy. ——
NDA 22-254; Lacosamide Injection: For the treatment of Epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older when oral administration is temporarily not feasible. Letter Date 9/28/07

Schwarz Biosciences, Inc.
P.O. box 110167
Research Triangle Park, NC 27709

Background

Schwarz Biosciences, Inc. requests approval for the marketing of lacosamide tablets for the treatment of epilepsy (NDA 22-253), lacosamide tablets for the management of neuropathic pain associated with diabetic peripheral neuropathy (NDA ——, lacosamide injection for the treatment of epilepsy(NDA 22-254) ——
——. In accordance with 21 CFR Part 25, Schwarz Biosciences, Inc. ha b(4)
submitted an Environmental Assessment (EA; dated June 2007) that evaluates the potential environmental impacts due to use and disposal of these products. The EA was submitted under NDA 22-253 and cross-referenced to NDAs 22-254 —— . The EA evaluates environmental introductions of lacosamide due to use and disposal of products to marketed under the —submitted NDAs.

[redacted]

b(4)

Discussion

The review appended below was conducted by Ruth Ganunis, Ph.D., under contract to the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (Completion date: May 11, 2008). Also attached are recommendations and an Executive Summary.

Comments and Conclusions

Based on an evaluation of the information provided in this EA and in FDA guidance, and on the scientific validity of the "no effects" conclusions of the EA, no significant adverse environmental impacts are expected from the introduction of lacosamide residues into the environment due to the use of lacosamide for the treatment of epilepsy and the management of neuropathic pain associated with diabetic peripheral neuropathy

A Finding of No Significant Impact (FONSI) is recommended.

EXECUTIVE SUMMARY – ENVIRONMENTAL ASSESSMENT

FONSI recommended.

After intake of lacosamide by patients for the treatment of partial-onset seizures or diabetic neuropathic pain, lacosamide is mainly excreted in human urine. There is one major metabolite, O-desmethyl lacosamide, which has no known activity. Lacosamide and the major metabolite O-desmethyl lacosamide are expected to reach the aquatic environment through POTWs. Lacosamide is highly water soluble, and has a low octanol/water coefficient (log Kow = 0.25). Adsorption/desorption experiments show low adsorption to soils and river sediment. The physicochemical data provided demonstrate that lacosamide will remain in the aquatic compartment, and that expose to the terrestrial and atmospheric compartments is expected to be insignificant. Forced degradation studies suggest that lacosamide is not likely to significantly degrade.

The maximum predicted amount of lacosamide manufactured for direct use in any of the next five years is [redacted] /year. Conservatively assuming no metabolism and no degradation in the environment for their analysis, the EIC is [redacted] µg/L. b(4)

The firm satisfied the requirements with tier 1 testing, which included microbial inhibition testing as well as acute testing on green algae. The EC_{50}/MEEC ratio for green algae growth is >10,000, which is greater than the assessment factor of 1000. To satisfy EU requirements, the firm also conducted chronic testing on zebra fish and *Daphnia*, and provided those results here. The most sensitive species identified in the chronic study is zebra fish, where the NOEC/MEEC ratio is >1000, which exceeds the tier 3 assessment factor of 10.

Based on the data, a FONSI can be recommended.

Recommendations:

A FONSI is recommended with the following qualifications:

- It is noted that the agency has requested a resubmission of the EA [redacted] b(4)

- The firm provided tier 1 testing for US requirements, and also provided tier 3 testing for EU requirements. They use the tier 3 assessment factor of 10 for comparison, although I am not sure that that assessment factor is appropriate because they did not provide the results of tier 2. The review is written assuming that use of the tier 3 factor in this case in appropriate. Either way they satisfy the tier 1 requirements and provide additional chronic studies for which the NOEC/MEEC ratio is significantly large that there is no environmental concern.

REVIEW OF ENVIRONMENTAL ASSESSMENT

1. **Date:** EA dated June 2007

2. **Name of applicant/petitioner:** Schwarz Biosciences, Inc

   ADEQUATE

3. **Address:**

   P.O. Box 110167
   Research Triangle Park, NC 27709

   ADEQUATE

4. **Description of the proposed action:**

   a. Requested Approval:

   NDA 22-253; Lacosamide Tablets, For the treatment of Epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older
   NDA [redacted] Lacosamide Tablets, For the management of neuropathic pain associated with diabetic peripheral neuropathy
   NDA 22-254; Lacosamide Injection, For the treatment of Epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older when oral administration is temporarily not feasible

   Lacosamide tablets will be marketed in 50 mg, 100 mg, 150 mg, 200 mg, 250 mg and 300 mg strengths packaged in HDPE bottles and PVC/PVDC aluminum blisters. Lacosamide 10 mg/ml solution for infusion will be packaged in clear glass vials with a rubber stopper and aluminum cap. Lacosamide 15 mg/ml syrup will be packaged in brown glass or PET bottles. An EA has been submitted pursuant to 21 CFR part 25.

   ADEQUATE

   b. Need for Action:

   Lacosamide is intended for use as a drug for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy, and management of neuropathic pain associated with diabetic peripheral neuropathy.

   ADEQUATE

c. Expected Locations of Use (Drug Product):
The locations of use will typically be hospitals, clinics and/or patients in their homes. The intravenous solution for infusion may also be used in emergency settings.

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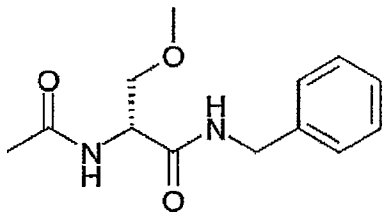
d. Disposal Sites

Empty or partially empty packages containing lacosamide 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
Established Name (USAN): Lacosamide
Proposed Trade Name: Not yet available
Chemical abstracts index name: Propanamide, 2-(acetylamino)-3-methoxy-N-(phenyl methyl)-, (2R)-
Systematic Chemical Name (IUPAC): (R)-2-Acetamido-N-benzyl-3-methoxypropionamide
Chemical Abstracts Service (CAS) Registration Number: 175481-36-4
Molecular Formula: $C_{13}H_{18}N_2O_3$
Molecular Weight: 250.3
Chemical Structure:



Lacosamide is the single (R)-enantiomer.

ADEQUATE

6. **Environmental Issue:**

a. Environmental Fate of Released Substances

i. Identification of Substances of Interest

After both oral and intravenous administration of lacosamide, 95% is recovered in urine and less than 0.5% in the feces. The major compounds excreted were unchanged lacosamide (40% of dose), O-desmethyl-metabolite (30% of dose), and a polar fraction (20%). Small amounts (0.5% to 2%) of further metabolites were found in the urine (listed page 9). The major metabolite, the O-desmethyl-metabolite, has no known pharmacological activity. The exact chemical structure of the polar fraction could not be determined, but it is likely that they are small polar molecules close to the R-serine backbone. It is assumed that the polar fraction has no pharmacological activity.

Additional stereo-specific analysis of urine samples showed that there is no enantiomeric interconversion of lacosamide.

Unchanged lacosamide, the O-desmethyl-metabolite, and the polar fraction account for approximately 90% of the dose. Since it is assumed that the metabolites do not have activity, and because the major metabolite, the O-desmethyl-metabolite, is expected to have comparable or higher water solubility than the parent compound, only the parent compound was studied in this EA as the substance relevant for the environmental risk assessment.

ADEQUATE

ii. Physical and Chemical Characterization

Test	Endpoint
Water solubility (25°C) in phosphate buffer, pH 4.5 in phosphate buffer, pH 7.5 in pure water	 Modification 1 : 28.4 mg/mL Modification 2 : 28.9 mg/mL Modification 1 : 20.1 mg/mL Modification 2 : 20.8 mg/mL Modification 1 : 30.2 mg/mL Modification 2 : 30.8 mg/mL
Log Kow (n-octanol / water partition coefficient) (OECD 107, shake flask method)	0.25 (mean, n=6)
Koc (adsorption / desorption coefficient normalized for organic carbon content of test soils) (OECD 106)	9 mL/g (adsorption) 12 mL/g (desorption)
Dissociation constant	No dissociation at environmentally relevant pH (pKa outside pH range of 1.5 to 12)
Vapour pressure at 25° C	$9.3 * 10^{-5}$ Pa (calculated)
Henry's Law Constant at 25°C	$1.14 * 10^{-11}$ atm*m³/mol (calculated)

Investigations on polymorphism of lacosamide show that the drug can be present in four different crystalline structures and one amorphous form. Two of the crystalline structures (modifications 1 and 2) are routinely formed in the regular synthesis of lacosamide drug substance and only these modifications are existent in lacosamide drug substance batches. Crystalline modifications 3 and 4, and the amorphous state only form under unique conditions or are not stable, and are not present in drug substance batches. b(4)

The log Kow was determined to be 0.25. A value less than 3 indicates that the compound is not likely to adsorb to the organic fraction of soil, sediment, or biosolids (i.e., sludge).

Although not required for EA submissions in the US, the adsorption/desorption coefficient was determined to satisfy the EU requirements and the data was reported in this EA. The adsorption value of 9 mg/g indicates a low potential of lacosamide to bind to the organic fraction of soils. The desorption values were slightly higher than the adsorption values, indicating reversibility of the adsorption process.

The physico-chemical data indicate that lacosamide is predominately present in the aqueous phase in undissociated form in the aquatic environment.

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iii. Environmental Depletion Mechanisms

Forced degradation studies were performed and their results are summarized below.

Environmental Depletion Mechanisms

Test	Result
Hydrolysis	Hydrolytically stable at environmentally relevant conditions, hydrolysis T½ > 24 hours
Photolysis	No significant degradation in solid state or aqueous solution after irradiation with 20,000 kJ/m^2 (1.2 million lux hours) or 100.000 kJ/m^2 (6 million lux hours) in aqueous solution.
Aerobic biodegradation (OECD 301 B, modified Sturm test)	Not readily biodegradable to carbon dioxide within 28 days under the stringent test conditions

Lacosamide is very stable at elevated temperatures and high humidity. Open and closed storage under accelerated conditions (40°C and 75% relative humidity) for 12 weeks showed no significant degradation of the substance.

Lacosamide is stable under environmentally relevant conditions. Abiotic degradation processes like hydrolysis, photolysis and thermal decomposition are not expected to contribute significantly to rapid dissipation of lacosamide from aquatic and terrestrial compartments.

Since no significant degradation processes were identified, no rapid depletion was assumed as a worst-case for assessment of the fate of lacosamide in the aquatic environment.

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iv. Environmental Concentration

The maximum predicted amount of lacosamide manufactured for direct use in any of the next five years is ——— year. Assuming no metabolism or environmental depletion, the firm determines the EIC to be — µg/L. b(4)

Taking a conservative approach, the firm assumes no dilution into surface waters after passage through POTWs. Therefore, the maximum expected environmental concentration (MEEC) was set to be equivalent to the EEC or EIC.

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v. Summary

Lacosamide is expected to enter the aquatic environment through patient use. Based on the high water solubility and low octanol/water coefficient (log Kow 0.25) no relevant partitioning into sewage sludge is expected.

Exposure in the terrestrial compartment is expected to be insignificant. Due to the low Kow of 0.25 and mean Koc of 9 mL/g no further testing on fate and effects in the terrestrial environment is indicated.

Due to the high water solubility of lacosamide and its low calculated vapor pressure and Henry's Law Constant there will be no substantive partitioning from the aquatic to the atmospheric compartment.

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b. Environmental Effects

Test	Result	NOEC/EIC
Inhibition of microbial respiration rate of activated sludge (OECD 209)	3-hour EC_{50} > 1000 mg/L 3-hour NOEC (EC_{15}) ≥ 1000 mg/L	>100,000
Effects on algal growth of green alga *Scenedesmus subspicatus* (OECD 201)	72-hour ErC50/EbC50 > 100 mg/L	>10,000
Fish Early Life Stage, Chronic test (OECD 210)	NOEC for all parameters tested ≥ 10 mg/L	>1,000
Daphnia Reproduction, Chronic test (OECD 211)	21-day NOEC was 32 mg/L on survival and reproduction rates of *Daphnia magna*	>10,000

The inhibitory effect of lacosamide on the respiration rate of aerobic wastewater microorganisms of activated sludge was investigated in a 3-hour respiration inhibition test following OECD Guideline 209. The 3 hour EC_{50} of lacosamide in the activated sludge respiration test was >1000. The 3 hour NOEC (EC_{15}) was ≥1000 mg/L.

Based on the log Kow <3.5 and the environmental fate data suggesting that lacosamide will remain in the aqueous phase, tier 1 acute toxicity testing in one aquatic species is appropriate. The firm provided the results of a 72 hour test on the growth of the green algal species *Scenedesmus subspicatus*. The test was conducted following OECD Guideline 201. The study found the 72-hour EC_{10} and EC_{50} are >100 mg/L. There were no sublethal effects observed at any dose tested; the NOEC was ≥100 mg/L. The EC_{50}/MEEC ratio for lacosamide is >10,000, which is larger than the tier 1 assessment factor of 1000.

To satisfy EU requirements, the firm included the results of chronic tests on *Daphnia* and zebra fish. An early life stage toxicity test on zebra fish was performed according to OECD Guideline 210. The test parameters assessed were egg development and hatching rate, time to hatch/development rate, survival of larvae and juvenile fish, and fish length and weight. For each test, the NOEC was ≥10 mg/L and the LOEC > 10 mg/L. Overall, the NOEC of lacosamide for early life stages of zebrafish was determined to be at least the highest test concentration of 10 mg/L. The NOEC/MEEC ratio for lacosamide in this test was 1,000, which is larger than the tier 3 assessment factor of 10.

The effect of lacosamide on the survival and reproduction of *Daphnia magna* was investigated according to OECD guideline 211. The test parameters assessed were mortality after 21 days and mean reproduction rate. The NOEC of lacosamide to *Daphnia magna* survival and reproduction was 32 mg/L. The

lowest concentration tested with toxic effects was 100 mg/L, the concentration where a statistically significant reduced mean reproduction rate was found. The NOEC/MEEC ratio for lacosamide in this chronic toxicity test was >10,000, which is significantly larger than the tier 3 assessment factor of 10.

c. Summary

After intake of lacosamide by patients for the treatment of partial-onset seizures or diabetic neuropathic pain, lacosamide is mainly excreted in human urine. Lacosamide and the major metabolite O-desmethyl lacosamide (which has no known activity) are expected to reach the aquatic environment through POTWs. The physicochemical data provided demonstrate that lacosamide will remain in the aquatic compartment, and that exposure of the terrestrial and atmospheric compartments is expected to be insignificant. Forced degradation studies suggest that lacosamide is not likely to significantly degrade. The firm takes a conservative approach by assuming no metabolism and no degradation in the environment for their analysis. While only tier 1 testing was required, the firm provided the results of chronic testing as well. The most sensitive species in the chronic test is zebra fish, where the NOEC/MEEC ratio is >1000, which far exceeds the tier 2 assessment factor of 10.

Based on the data, a FONSI can be recommended.

ADEQUATE

7. Mitigation Measures

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

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8. Alternatives to the proposed action

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

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9. List of Preparers

Names and professional experience are provided.

ADEQUATE

10. References

References are provided.

ADEQUATE

11. Appendices

Provided.

ADEQUATE

Review by: Ruth Ganunis, Ph.D., May 11, 2008
Under contract to:
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

Raanan Bloom
5/15/2008 01:08:37 PM
ENV ASSESSMENT

Jon E. Clark
5/15/2008 02:08:15 PM
CHEMIST

ENVIRONMENTAL ASSESSMENT

and

FINDING OF NO SIGNIFICANT IMPACT

for

Lacosamide Tablets

NDA 22-253

Food and Drug Administration
Center for Drug Evaluation and Research

Date Completed: May 11, 2008

[redacted]

FINDING OF NO SIGNIFICANT IMPACT

NDA 22-253

Lacosamide Tablets

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 impact on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of its new drug application for Lacosamide, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg and 300 mg tablets, Schwarz Bioscience, Inc. prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product.

Lacosamide is intended for use as a drug for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy, and management of neuropathic pain associated with diabetic peripheral neuropathy.

Lacosamide may enter the environment from patient use and disposal. It is expected to enter into the aquatic environment. Data indicate that the compound is unlikely to enter the terrestrial and atmospheric environments. The toxicity of lacosamide to aquatic organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at expected environmental concentrations.

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

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

PREPARED BY:

Ruth Ganunis, Ph.D.
under contract to
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

CONCURRED BY:

Raanan A. Bloom, Ph.D.
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CONCURRED BY:

Jon Clark, M.S.
Associate Director for Policy
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

CONCURRED BY:

Moheb Nasr, Ph.D.
Director, Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment:

Environmental Assessment dated June, 2007
Appended Electronic Signature Page

ENVIRONMENTAL ASSESSMENT (EA)

OF LACOSAMIDE

EXPERT REPORT

TABLE OF CONTENTS

SIGNATURES

The present Environmental Assessment Expert Report was prepared by:

Environmental Expert:

June 26, 2007 .....

Date Dr. Enrico Kiefer
RCC Ltd.

Sponsor's Representative:

June 28, 2007 .....

Date Dr. Niels Krebsfänger, D.A.B.T.
SCHWARZ BIOSCIENCES GmbH

1 DATE

Date of EA preparation: **June, 2007**

Date of subsequent amendment(s): --

2 NAME OF APPLICANT OR PETITIONER

SCHWARZ BIOSCIENCES, Inc.

3 ADDRESS

P.O. Box 110167

Research Triangle Park, NC 27709

8010 Arco Corporate, Suite 100

Raleigh, NC 27617

USA

4 DESCRIPTION OF PROPOSED ACTION

4.1 Requested Approval

Schwarz Biosciences, Inc. has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for lacosamide tablets (50 mg, 100 mg, 150 mg, 200 mg, 250 mg, and 300 mg) packaged in HDPE bottles and PVC/PVDC aluminum blisters, lacosamide 10 mg/ml solution for infusion packaged in clear glass vials with rubber stopper and aluminum cap, and lacosamide 15 mg/ml syrup packaged in brown glass or PET bottles. An EA has been submitted pursuant to 21 CFR part 25.

4.2 Need for Action

Lacosamide is intended for use as drug for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy, and management of neuropathic pain associated with diabetic peripheral neuropathy.

4.3 Locations of Use

The locations of use will typically be hospitals, clinics and/or patients in their homes. The intravenous solution for infusion may also be used in emergency settings.

4.4 Disposal Sites

At U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures in accordance with local requirements. In the home, 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, although minimal quantities of the unused drug could be disposed of in the sewer system.

5 IDENTIFICATION OF SUBSTANCE THAT IS THE SUBJECT OF THE PROPOSED ACTION

5.1 Nomenclature

5.1.1 Established Name (INN/USAN/Laboratory Codes and Previous Names)

International Nonproprietary Name (INN):
Lacosamide

United States Adopted Name (USAN):
Lacosamide

Laboratory Codes and Previous Names:
SPM 927, ADD 234037, harkoseride

5.1.2 Brand/Proprietary Name/Trade Name

Not yet available.

5.1.3 Chemical Names

Chemical Abstracts (CA) Index Name:
Propanamide, 2-(acetylamino)-3-methoxy-N-(phenyl methyl)-, (2R)-

Systematic Chemical Name (IUPAC):
(R)-2-Acetamido-N-benzyl-3-methoxypropionamide

5.2 Chemical Abstracts Service (CAS) Registration Number

175481-36-4

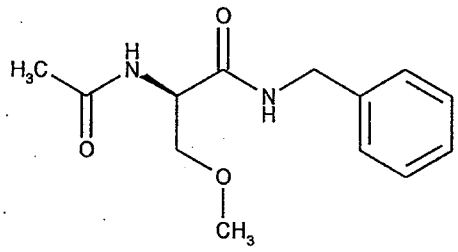
5.3 Molecular Formula

$C_{13}H_{18}N_2O_3$

5.4 Molecular Weight

250.3

5.5 Structural Formula



Lacosamide is the single (R)-enantiomer.

APPEARS THIS WAY
ON ORIGINAL

6 ENVIRONMENTAL ISSUES

6.1 Environmental Fate of Released Substances

6.1.1 Identification of Substances of Interest

Human metabolism and excretion of lacosamide is described in CTD Module 2.7.2.3.3 and CTD Module 2.7.2.3.4, respectively, and briefly summarized below.

After oral and intravenous administration of 100 mg [^{14}C]-lacosamide (45 µCi) in healthy subjects, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the feces. The major compounds excreted were unchanged lacosamide (SPM 927, approximately 40% of the dose) and its O-desmethyl-metabolite (SPM 12809, approximately 30%). A polar fraction accounted for approximately 20%. Small amounts (0.5 to 2%) of further metabolites were found in the urine: the p-hydroxy-, the O-desmethyl-p-hydroxy-, O-desmethyl-m-hydroxy-, and the desacetyl derivatives of lacosamide. In addition, a N-carbamoyl-O-ß-D-glucuronide of the desacetyl metabolite has been identified. In plasma the O-desmethyl metabolite SPM 12809 represents approximately 10% of the parent compound. In conclusion the major human metabolite is SPM 12809. This metabolite has no known pharmacological activity.

Additional stereo-specific analysis of urine samples showed that there is no enantiomeric interconversion of lacosamide.

With regard to the structure of the polar fraction, the analytical results do not allow evident proposals for exact chemical structures, though they indicate small polar molecules close to the R-serine backbone. This seems to be most probable since larger molecules could not be observed in the respective MS-spectra and the expressed polar chromatographic behavior indicates loss of lipophilic structural elements.

The findings of the metabolism/excretion study show that excretion of unchanged lacosamide and the metabolites formed mainly occurs via urine (approximately 95% of applied dose). Thus, the substances of interest for the environmental assessment are besides unchanged lacosamide the major O-desmethyl metabolite SPM 12809 and a polar fraction, which potentially can reach surface waters (aquatic environment) via sewage systems. These compounds account for approximately 90% of the dose. The major metabolite (O-desmethyl metabolite, SPM 12809) in humans has no known pharmacological activity. All other metabolites found in urine were below 2% and are like the polar fraction assumed to be also pharmacologically not active. Physico-chemical data on the major human metabolite SPM 12809 (O-desmethyl lacosamide) are not available. But concluding from its chemical structure (i.e., due to de-masking of a polar hydroxy group) and the retention times in HPLC-runs the substance is considered more polar than lacosamide, and therefore expected to have a comparable or higher water solubility than the parent compound. Thus, only the parent compound, i.e. the active moiety lacosamide, was studied in this EA as the substance relevant for the environmental risk assessment.

6.1.2 Physical and Chemical Characterization

The table in Appendix 11.1.1 lists the physico-chemical properties of lacosamide (see also CTD Module 3.2.S.1.3 and CTD Module 3.2.S.3.1).

6.1.2.1 Polymorphism

Investigations on polymorphism of lacosamide have shown that the drug substance can be present in more than one crystalline structure. Four different crystalline structures and one amorphous form were identified (CTD Module 3.2.S.1.3). Two of the crystalline structures (modifications 1 and 2) are routinely formed in the regular synthesis of lacosamide drug substance and only these modifications are existent in lacosamide drug substance batches. Modification 3 is a crystalline, metastable modification that appears only by crystallization from methylene chloride at room temperature. The fourth modification (modification 4) is stable only up to -120°C and converts to modification 1 above -120°C. The amorphous state is widely unstable under normal laboratory conditions and converts rapidly to a crystalline modification.

6.1.2.2 Water Solubility

Solubility measurements were performed in aqueous solutions with modification 1 and 2 at 37°C and 25°C. The water solubility for both modifications was comparable, ranging from 28.4 to 28.9 g/L in phosphate buffered aqueous solutions at pH 4.5 at 25° C. In phosphate buffered solutions of pH 7.5 solubilities were slightly lower ranging from 20.1 to 20.8 g/L at 25°C. In pure water the measured solubilities were in the range of 30.2 to 30.8 g/L
(CTD Module 3.2.S.1.3 and CTD Module 3.2.S.3.1).

6.1.2.3 Octanol / Water Partition Coefficient (log Kow)

The n-octanol / water partition coefficient was determined at 20°C using the shake flask method (CTD Module 3.2.S.1.3 and CTD Module 3.2.S.3.1). The concentration of lacosamide in the octanol and water phase was determined by HPLC. Although not explicitly stated in the report the experiment followed the testing principles of OECD test guideline 107 (shake flask method). The partition coefficient (log Kow) was determined to be 0.25 (mean value of 6 determinations from different n-octanol / water ratios).

6.1.2.4 Adsorption / Desorption Coefficient (Koc)

Since log Kow was determined to be less than 3 (Section 6.1.2.3) no further study on adsorption / desorption properties is required as per the *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July, 1998)*. However, the adsorption / desorption coefficient (Koc) has been determined to satisfy European Union requirements and is reported below.

The adsorption / desorption behavior of [^{14}C]- lacosamide was investigated on four soils (soil I, II, III and V) and one river sediment (soil IV) differing in their organic matter content, cation exchange capacity, pH and particle size (CTD Table 2.6.7.17, A22206). The test was done under GLP following the batch equilibrium method according to OECD test guideline 106. In preliminary tests for determination of the soil to solution ratios and the equilibration time some instability of lacosamide was observed in the supernatants of the soil I and II after 48 hours of adsorption. In order to minimize degradation the soils were sterilized by γ-irradiation (soil I, II, III and V) for the screening tests. Sterilization of the sediment was considered not necessary since a pre-test under non-GLP conditions showed the stability of the compound in this test system.

The screening tests were conducted with all soils/sediment at a concentration of 0.05 mg/L and at a soil/solution ratio of 1:1. After 2, 5, and 24 hours of shaking, the amount adsorbed was determined for all soils/sediment. After 24 hours of incubation 11.3%, 20.4%, 11.4%, 10.9% and 12.2% of the amount applied was adsorbed for soils I to V, respectively.

The desorption was subsequently performed after the adsorption step. The test item concentration in the supernatant was determined for all soils/sediment after 2, 5, 24 and 48 hours. The desorption equilibrium was reached very fast (i.e. within not more than five hours).

HPLC analyses of the supernatants of adsorption and desorption experiments showed, that lacosamide remained stable under the test conditions (i.e. using soils sterilized by γ-irradiation).

The following adsorption/desorption coefficients normalized for organic carbon content of the soils/sediment were determined (K_{OC}):

Soil	Soil I (loam)	Soil II (clay loam)	Soil III (silty clay loam)	Soil IV (sandy loam) [River sediment]	Soil V (silt loam)	Mean values
K_{OC} (mL/g)	10	6	5	16	7	9
$K_{des,OC}$ (mL/g)	16	9	5	20	10	12

A mean adsorption K_{OC} of 9 mL/g and a mean desorption $K_{des,OC}$ of 12 mL/g was calculated. The calculated $K_{des,OC}$ values were slightly higher than those obtained for the adsorption isotherms, indicating reversibility of the adsorption process. Only a small part of radioactivity (less than 4%) could not be extracted with organic solvents and therefore, remained bound to the soil.

6.1.2.5 Dissociation Constant (pKa)

The dissociation constant in water was determined by potentiometric (conductometric) titration (CTD Module 3.2.S.1.3 and CTD Module 3.2.S.3.1). No pKa value could be determined for lacosamide drug substance within the measured pH range of 1.5 to 12. It is concluded that there is no relevant dissociation of SPM 927 at pH relevant in the environment.

6.1.2.6 Vapor Pressure and Henry's Law Constant

The vapor pressure of lacosamide was calculated to be 9.3×10^{-5} Pa at 25°C based on an estimated boiling point of 334°C, and using the Modified Watson Correlation. From this calculated vapor pressure and based on the lowest reported solubility of 20.1 g/L a Henry's Law Constant of $1.14 * 10^{-11}$ atm*m^3/mol was estimated for aqueous phosphate buffered solution at pH 7.5 (3.2.S.1.3).

6.1.2.7 Conclusion

The physico-chemical characterization of lacosamide (water solubility of > 20 g/L, Henry's Law Constant of $1.14 * 10^{-11}$ atm*m^3/mol, log Kow of 0.25, no relevant dissociation at environmentally relevant pH) indicate the substance to be predominantly present in the water phase in undissociated form in the aquatic environment. This is further supported by a mean K_{OC} of 9 mL/g indicating a low potential of lacosamide to bind to the organic fraction of soils, sediments and biosolids (i.e., sludge).

The potential for bioconcentration is considered to be low (log Kow < 3.5), and tier 1 acute toxicity testing in one aquatic species should be performed, i.e. no further testing on bioconcentration, terrestrial species or chronic toxicity testing is triggered according to the *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July, 1998)*.

Physico-chemical data on the major human metabolite SPM 12809 (O-desmethyl lacosamide) are not available. However, concluding from its chemical structure (i.e., due to de-masking of a polar hydroxy group) and the retention times in HPLC-runs the substance is considered more polar than lacosamide, and therefore expected to have a comparable or higher water solubility than the parent compound.

6.1.3 Environmental Depletion Mechanisms

6.1.3.1 Forced Degradation Studies

Forced degradation studies with lacosamide were performed to evaluate the stability of the substance under various stress conditions (CTD Module 3.2.S.7.3).

Temperature and Humidity

Lacosamide was found to be very stable at elevated temperatures and high humidity. Open storage of lacosamide for 71 days at 120°C showed only little degradation of the substance. Degradation products observed at the end of the experiment accounted in total for ≤ 0.3%. Open and closed storage under accelerated conditions (40°C and 75% relative humidity) for 12 weeks showed no significant degradation of the substance.

Photolysis

In photostability tests lacosamide proved to be stable in solid state and in aqueous solution after irradiation with 20'000 kJ/m^2 (1.2 million lux hours) in a SUN-TEST apparatus. Even after irradiation with 100.000 kJ/m^2 (6 million lux hours) in aqueous solution in quartz vials lacosamide accounted for 99.95 % of the initial concentration.

Hydrolysis

In aqueous solutions at moderate acidic (pH 3) and at neutral conditions (pH 7) a decrease of lacosamide of 2-5% was observed after 4 weeks storage at 60°C. Under strong acidic (pH 1) and alkaline conditions (pH 10) at a temperature of 60°C the substance rapidly decomposed (in 0.1 N NaOH quantitative degradation was observed after 24h). Moderate degradation was reported after addition of 3% hydrogen peroxide to aqueous solutions of pH 3, pH 7 and pH 10. After 24 hours storage at room temperature (25°C) under oxidizing conditions a decrease of 2-6% of lacosamide was reported.

Conclusion

The results of the forced degradation studies indicate lacosamide to be stable under environmental relevant temperature and pH conditions. Abiotic degradation processes like hydrolysis, photolysis and thermal decomposition are not expected to contribute significantly to rapid dissipation of lacosamide from aquatic and terrestrial compartments after entry into the compartment.

6.1.3.2 Ready Biodegradability

Lacosamide was investigated for its ready biodegradability in a 28-day CO_2 evolution test (Modified Sturm test, OECD Guideline for Testing of Chemicals, No. 301 B (1992)). The test was conducted under GLP (CTD Table 2.6.7.17, A22173).

In this test evolution of CO_2 within 28 days was measured after adding lacosamide at a concentration of 25 mg/L (equivalent to 15.6 mg TOC/L) to the test medium including as an inoculum's activated sludge from a wastewater treatment plant. The toxicity of lacosamide to the

inoculum was tested before in a microbial respiration inhibition test (CTD Table 2.6.7.17, A27033; see Section 6.2.1). Lacosamide was found to have no inhibitory effect on the respiration rate of activated sludge after 3 hours incubation up to 1000 mg/L (highest concentration tested).

In the test on ready biodegradability the carbon dioxide formed after addition of lacosamide to the inoculated test medium was trapped in adsorber flasks containing NaOH and sampled at different time intervals up to 28 days. The samples were analyzed for inorganic carbon (IC) using a TOC analyzer.

The CO_2 production of the test item lacosamide in the test media was 3-4% at the end of the test (day 28) and thus only slightly higher than in the inoculum controls. According to the respective OECD Guidelines, based on ultimate biodegradation (i.e. CO_2 evolution), lacosamide has to be considered to be not readily biodegradable under the test conditions.

In comparison, the reference item (sodium benzoate) was degraded to an average extent of 76% by exposure Day 14 in procedure controls, confirming the validity of the test conditions (>60% degradation by Day 14). By the end of the test the reference substance was completely degraded. In controls containing lacosamide and test medium de-activated by addition of mercury dichloride, no degradation was noted at the end of the 28-day exposure period.

However, the ready biodegradability test measuring as an endpoint formation of CO_2 does not give information on the inherent biodegradability of test substances when the test substance is not extensively degraded to carbon dioxide within the test period.

6.1.3.3 Conclusion

Since no significant degradation processes were identified so far no rapid depletion due to abiotic or biotic degradation was assumed as a worst-case for assessment of the fate of lacosamide in the aquatic environment.

6.1.4 Environmental Concentrations

6.1.4.1 Expected Introduction Concentration (EIC)

The expected introduction concentration (EIC) of lacosamide (SPM 927) into the aquatic environment was calculated according to the equation given in the *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications, Section III.A.2 (July, 1998)*:

EIC-Aquatic (ppb) = A x B x C x D

Where

A= kg/year produced for direct use (as active moiety) in any of the next 5 five years (i.e. based on sales forecast for years 2008 to 2012; Appendix 11.2.1)

B= 1/litres per day entering POTWs

(1.214 x 10^{11} liters per day entering publicly owned treatment works (POTWs, Source: 1996 Needs Survey, Report to Congress)

C= year/365

D= 10^{9} µg/kg (conversion factor)

For calculation of the EIC for lacosamide it was assumed that

- All quantities of lacosamide in drug products produced in a year for treatment of partial-onset seizures and diabetic neuropathic pain are used and enter the POTW system.
- Drug product usage occurs throughout the United States in proportion to the population and amount of wastewater generated.
- There is no metabolism (i.e. the active moiety corresponds to unchanged lacosamide).
- There is no significant environmental depletion in the waste treatment process.

Under these conservative assumptions the EIC exceeds 1 ppb (µg/L) at the point of entry into the aquatic environment (Appendix 11.2.2). Accordingly, the drug application is subject for preparation of an EA.

6.1.4.2 Expected Environmental Concentration (EEC, MEEC)

For deriving the expected environmental concentration (EEC) for the aquatic compartment no dilution or degradation was assumed as a conservative first tier estimate for lacosamide entering surface waters after passage of POTWs. **Thus, the maximum expected environmental concentration (MEEC) was set to be equivalent to the EEC or EIC in a conservative approach (Appendix 11.2.3).**

6.1.5 Summary on Environmental Fate of Released Substances

6.1.5.1 Aquatic Compartment

The expected introduction concentration (EIC) of lacosamide into the aquatic environment was calculated based on the fifth-year marketing estimate assuming all quantities produced in a year are used and enter POTWs as active moiety. Under this conservative assumption the EIC exceeds 1 ppb (µg/L) at the point of entry into the aquatic environment and the drug application is subject for preparation of an EA. For estimation of the EEC (expected environmental concentration) in a first tier no depletion mechanisms, metabolism in humans or dilution was assumed to reduce the concentration in water. In this conservative approach, the maximum expected environmental concentration (MEEC) is thus considered to be equivalent to the EEC or EIC.

After intake of lacosamide by patients for treatment of partial-onset seizures or diabetic neuropathic pain the substance is mainly excreted in the human urine. Besides unchanged lacosamide (approximately 40% of applied dose) the major metabolite (O-desmethyl lacosamide) and a polar fraction were found in human urine exceeding 10% of applied dose. The O-desmethyl metabolite (SPM 12809) has no known pharmacological activity. These substances may reach the aquatic environment (surface water) by transport via sewage and sewage works (POTWs).

In the aquatic environment once entered lacosamide is mainly present in the aqueous phase. Concluding from its high water solubility and low octanol/water coefficient (log Kow 0.25) no relevant partitioning into sewage sludge or sediment is expected. Although not required, this is confirmed by adsorption / desorption experiments showing low adsorption to the soils and the river sediment tested (mean Koc of 9 mL/g). A similar behavior is assumed for the major urine metabolites for which chemical structures and HPLC retention times indicate to be more polar thus to have a comparable or higher water solubility than the parent molecule.

Forced degradation studies with lacosamide indicate that abiotic processes like hydrolysis or photolysis do not contribute significantly to the depletion of lacosamide from the aquatic environmental compartment. In a ready biodegradability test lacosamide was not readily degraded to carbon dioxide under the given stringent test conditions. However, it is assumed that the compound is degraded to some extent under more realistic test conditions in the aquatic environment. For the present EA, in a conservative approach, it was assumed that the compound and its major urine metabolites are stable in surface water once they have entered the aquatic environment.

6.1.5.2 Terrestrial Compartment

Exposure of the terrestrial compartment is expected to be insignificant if the usual recommendations for disposal of unused drugs and empty packages are followed. Since lacosamide and its major urine metabolites are predominantly present in the aqueous phase partitioning into sludge of wastewater treatment plants will be negligible. No relevant exposure

is therefore expected from spreading of sludge on agricultural land for fertilization. Due to the low Kow of 0.25 and mean Koc of 9 mL/g no further testing on fate and effects on the terrestrial environment is indicated.

6.1.5.3 Atmospheric Compartment

Substantive volatilization from the aquatic or terrestrial environment to the atmospheric environment is not expected for lacosamide and its major urine metabolites. Due to the high water solubility of lacosamide and its low calculated vapor pressure and Henry's Law Constant there will be no substantive partitioning from the aquatic to the atmospheric compartment. Further, medical indications of lacosamide do not include applications as aerosol spray or medical gases and therefore exposure of air is considered to be not relevant.

6.2 Environmental Effects of Released Substances

6.2.1 Microbial Inhibition Testing

The inhibitory effect of lacosamide on the respiration rate of aerobic wastewater microorganisms of activated sludge was investigated in a 3-hour respiration inhibition test according to OECD Guideline for Testing of Chemicals, No. 209. The test was done under GLP (CTD Table 2.6.7.17, A27033).

Test Design

Test species:	Aerobic activated sludge collected from a wastewater treatment plant (ARA Ergolz II, Füllinsdorf, Switzerland) treating mainly domestic wastewater.
Test conditions:	2000 mL glass beakers; test medium: synthetic wastewater (feed solution), activated sludge inoculum, and test item at a final volume of 500 mL; suspended solid concentration: 1.2 g dry material/L; aerated for 3 hours at 20°C; pH 7.6 – 8.5
Test concentrations:	Nominal concentrations of lacosamide of 10, 32, 100, 320, and 1000 mg/L were tested. In addition, two non-treated negative controls and three different concentrations of the reference item 3,5-dichlorophenol (5, 16 and 50 mg/L) were tested in parallel. The results of these treatments confirmed the suitability of the activated sludge and the method used.
Test endpoints:	Assessment of the inhibitory effect of the test item on the oxygen consumption rate of aerobic micro-organisms (activated sludge) after short-term exposure of 3 hours. The median effective concentration (3-hour EC_{50}) for the reference item (3,5-dichlorophenol) was calculated by Probit analysis.

Findings

Up to and including the concentration of 1000 mg/L the test item had no inhibitory effect (<15%) on the respiration rate of activated sludge after the incubation period of three hours (Table). Thus, the 3-hour NOEC (EC_{15}) of lacosamide to activated sludge microorganisms was at least 1000 mg/L. This value might even be higher, but concentrations in excess of 1000 mg/L were not tested. The 3-hour EC_{20}, EC_{50} and EC_{80} could not be calculated, but were clearly higher than 1000 mg/L.

The EC_{50} of the reference item 3,5-dichlorophenol (13 mg/L) was within the range of 5 to 30 mg/L as required by the OECD Guideline 209 confirming the suitability of the test system.

Influence of Lacosamide on Oxygen Consumption of Activated Sludge

Test chemical	Nominal concentration of test chemical (mg/L)	Oxygen consumption rate (mg O_2/L min^{-1})	Inhibition (%)
Control	0	1.155	
Control	0	1.218	
Mean		1.186	
Deviation (%)		5.5	
SPM 927	10	1.184	0.2
SPM 927	32	1.253	-5.7
SPM 927	100	1.232	-3.9
SPM 927	320	1.246	-5.0
SPM 927	1000	1.204	-1.5

Conclusion

The 3-hour EC_{50} of lacosamide in the activated sludge respiration inhibition test was >1000 mg/L. The **3-hour NOEC (EC_{15}) was ≥1000 mg/L. The 3-hour NOEC exceeds by far (>100'000x) the EIC** (environmental introduction concentration) estimated at the point of entry of lacosamide into POTWs via sewage (Appendix 11.2.4.1).

6.2.2 Effects on Aquatic Organisms: Tier 1 Testing

Based on the low potential for bioconcentration (log Kow < 3.5; Section 6.1.2.7) and the overall assessment of lacosamide's environmental fate indicating exposure mainly of the aqueous phase of the aquatic compartment (Section 6.1.5), tier 1 acute toxicity testing in one aquatic species is appropriate per *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998).* One suitable test proposed is an algal species bioassay.

6.2.2.1 Effects on growth of *Scenedesmus subspicatus*

The influence of the test item lacosamide on the growth of the green algal species *Scenedesmus subspicatus* CHODAT was investigated in a 72-hour static test according to OECD Guideline No. 201, 1984. The test was conducted under GLP (CTD Table 2.6.7.17, A22184).

Test Design

Test species:	Green alga *Scenedesmus subspicatus* CHODAT (Strain No. 86.81); Source: SAG (Culture Collection of Algae) Göttingen, Germany.
Test design:	1 concentration with three replicates and a blank test medium control group with 6 replicates were tested under static conditions for 72 hours.
Test concentration:	nominal 100 mg lacosamide/L, a limit test was done based on the results of a range finder test.
Inoculum at test start:	Nominal 1 x 10^4 cells/mL from a 4-day old exponentially growing pre-culture.
Test conditions:	Volumes of 15 mL algal suspension for each replicate were continuously stirred by magnetic stirrers in 50 mL Erlenmeyer flasks. The flasks were covered with glass dishes, incubated in a temperature controlled water bath at a temperature of 22 °C, and continuously illuminated at a measured light intensity of about 7400 Lux (mean value). The pH at 0 and 72 hours was 8.2 and 8.5 for both control and treated sample.
Dosage:	A single test item concentration of nominal 100 mg/L was tested. Additionally, a control was tested in parallel (test water without addition of the test item). The test medium of nominal 100 mg/L was prepared by dissolving 69.8 mg of test item completely in 700 mL of test water using ultrasonic treatment and intense stirring (5 minutes each) at room temperature. The test concentration was based on the results of a range-finding test (without GLP). Concentrations in excess of nominal 100 mg/L have not been tested in compliance with EU Commission Directive 92/69/EEC (limit test).
Analytics:	Concentrations of the test substance were measured by means of HPLC at test start and after 72 h.

Observations:	Algal cell densities in the samples were determined by counting with an electronic particle counter, at least two measurements per sample. In addition, shape and size of the algal cells was examined microscopically in samples taken from the control and the single test concentration after 72 hours exposure.
Endpoints/Statistics:	Inhibition of algal growth was determined from the mean values of counted algal cell densities. The test concentrations corresponding to 10 and 50% inhibition of the algal biomass b (E_bC_{10}, E_bC_{50}), or of the growth rate r (E_rC_{10}, E_rC_{50}) could not be calculated due to the absence of a toxic effect of the test item. LOEC and NOEC were determined directly from the counted algal cell densities. The mean cell densities were tested on significant differences to the control values by the STUDENT-t-test ($\alpha = 0.05$, one sided smaller).

Findings

The analytically determined test item concentration in the analyzed test medium ranged from 91 to 93% of the nominal value. Consequently, the test item was stable during the test period of 72 hours under the conditions of the test, and the reported biological results are based on the nominal concentration of the test item.

The test item lacosamide clearly had no inhibitory effect on the growth of *Scenedesmus subspicatus* during the exposure period of 72 hours at the test concentration of 100 mg/L. The 72-hour NOEC (highest concentration tested without toxic effects after the exposure period of 72 hours) of lacosamide to *Scenedesmus subspicatus* was therefore determined to be at least 100 mg/L. This value might even be higher, but concentrations in excess of 100 mg/L have not been tested according to EU Commission Directive 92/69/EEC.

The 72-hour LOEC (lowest concentration tested with toxic effects after the exposure period of 72 hours) and the 72-hour EC_{10} and EC_{50} for the algal biomass b and growth rate r could not be quantified due to the absence of a toxic effect of lacosamide at the tested concentration. Accordingly, these parameters are clearly higher than 100 mg/L.

Upon microscopic examination there were no obvious effects on the shape and size of the algal cells growing in the test medium at the nominal concentration of 100 mg/L after 72 hours exposure.

Conclusion

The 72-hour EC_{10} and **EC_{50} are >100 mg/L** and there were no sublethal effects observed at any dose tested, i.e. the NOEC was ≥100 mg/L. **The EC_{50}/MEEC ratio for lacosamide in this tier 1 test clearly exceeds a factor of 1000** (>10'000; Appendix 11.2.4.2). Thus, no higher tier testing (tier 2 or 3 testing) is required per *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998).*

6.2.3 Effects on Aquatic Organisms: Higher Tier Testing

Although higher tier testing (tier 2 or 3 testing) for lacosamide is not required per *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998)* as discussed in Section 6.1.2.7, Section 6.2.2 and Section 6.3, an early life stage toxicity test in zebra fish and a reproduction test in daphnids were performed to satisfy European Union requirements. Data from those supplementary chronic toxicity tests are presented in this section for information on the ecotoxicity data available on lacosamide.

6.2.3.1 Effects on Fish Early Life Stage

The toxicity of the test item lacosamide to zebra fish (*Brachydanio rerio*) was investigated in an early life stage toxicity test according to the OECD Guideline for Testing of Chemicals, No. 210, "Fish, Early-life Stage Toxicity Test", 1992. (CTD Table 2.6.7.17, A45180)

Test Design

Test species:	The study was performed with newly fertilized eggs from zebra fish, *Brachydanio rerio* (Hamilton-Buchanan 1822, Teleostei, Cyprinidae). The origin of the strain of zebra fish is West Aquarium GmbH, D-37431 Bad Lauterberg, Germany. In the laboratories of RCC a brood batch of at least 200 individuals of this strain was held.
Test design:	A flow through system was used for the exposure of the eggs, larvae and fish. Depending on the size of the fish, glass vessels up to 2.0 liter volume were used. Four replicates were used for each test concentration and the control. 60 freshly fertilized eggs were exposed to four replicates of each test concentration and the control (15 eggs per replicate). The test duration was 5 days post fertilization plus 30 days post-hatch, in total 35 days.
Test concentration:	Nominal 0.10, 0.32, 1.0, 3.2, and 10 mg lacosamide/L, in parallel with a control. Test concentrations were based on the results of a range finder test.
Test conditions:	The test was conducted in reconstituted water with water hardness of 1.25 mmol/L (= 125 mg/L) as $CaCO_3$ pH values in the test media ranged from 7.0 to 7.1, dissolved oxygen concentrations were at least 6.6 mg/L. Water temperature ranged from 25.6 to 26.4 °C. Photoperiod was 16 hours light and 8 hours darkness. Test animals were fed ad libitum each day with live rotifers, live nauplia of *Artemia salina* and/or commercial dry fish food.
Dosage:	In this flow-through test, the concentrations of the test item in the test media were maintained by dosing application solution (= concentrated test item solutions) into the test water by using automatic dispenser

	units (HAMILTON, Reno, Nevada, USA). The test media were divided into four identical volumes by electronically regulated splitting devices (PEQUITEC, CH-4414 Füllinsdorf, Switzerland) and were directed to the four replicates of each treatment. The flow rate of the test media through each of the four replicate glass beakers corresponded to at least a fivefold theoretical volume exchange per day. The application solution used for the dosage of the highest test concentration was prepared by dissolving the test item completely in purified water. In a series of dilution steps, this test medium was diluted with test water to prepare the application solution used for the dosage of the lower test concentrations.
Analytics:	From the application solutions, all test media and the control duplicate samples were taken regularly during the test period. The concentrations of lacosamide were analyzed by HPLC in the test media samples from the highest test concentration of nominal 10 mg/L, determined in the experiment as the NOEC.
Observations:	The embryonic development and hatching of larvae in the control and the test concentrations was recorded each day. Larvae and juvenile fish were observed for mortality and visible abnormalities. At the end of the test the fish length, the body wet weight and the dry weight of the fish was determined.
Endpoints/Statistics:	Percent hatching success (hatching rate) was calculated for each replicate by dividing the number of hatched larvae by the number of eggs inserted. The mean development rate was calculated for each treatment. The survival rate of the test fish was calculated for each test concentration and the control by dividing the number of surviving fish by the number of larvae hatched. The LOEC and the NOEC for all parameters assessed were determined directly from the raw data. A statistical evaluation was not necessary since the results obtained from the different test concentrations were nearly equal or even slightly higher compared to the control.

Findings

The analytically measured lacosamide concentration in the test medium of 10 mg/L was in the rage of 95 to 110% of the nominal value during the exposure period. The test concentration was shown to be constant during the entire test period and therefore all biological results are related to the nominal concentrations of 10 mg/L.

The biological results at test end are given for each test parameter assessed:

Test parameter	NOEC*) (mg/L)	LOEC*) (mg/L)
Egg development and hatching rate	≥ 10	> 10
Time to hatch / development rate	≥ 10	> 10
Survival of larvae and juvenile fish	≥ 10	> 10
Fish length and weight (wet weight and dry weight) at test end	≥ 10	> 10

*) based on nominal test item concentrations

Conclusion

Summarizing the NOECs for each of the test parameters assessed, the **overall NOEC of lacosamide for early life stages of zebra fish was determined to be at least the highest test concentration of 10 mg/L.** The NOEC might be even higher, but concentrations above nominal 10 mg/L were not tested according to the guideline. The overall LOEC was determined to be >10 mg/L. **The NOEC/MEEC ratio for lacosamide in this chronic toxicity test by far exceeds a factor of 10** (>1'000; Appendix 11.2.4.3).

6.2.3.2 Effects on Reproduction of *Daphnia magna*

The effect of the test item lacosamide on the survival and reproduction of the aquatic invertebrate *Daphnia magna* was investigated in a semi-static test over 21 days following the OECD Guidelines for Testing of Chemicals, No. 211, (1998): "*Daphnia magna* Reproduction Test" (CTD Table 2.6.7.17, A45202)

Test Design

Test species:	Young female daphnids (less than 24 hours old) of a clone of the species *Daphnia magna* Straus. A clone (originally supplied by the University of Sheffield/UK) is bred in RCC's laboratories in culture medium identical to the medium used for the test.
Test design:	21 days semi-static test with test medium renewal periods of two and three days. 10 daphnids per test concentration and control were used, each test animal individually kept in 80 mL of test medium.
Test concentration:	Nominal 1.0, 3.2, 10, 32 and 100 mg lacosamide/L, in parallel with a control. Test concentrations were based on the results of a range finder test.
Test conditions:	The test was conducted in reconstituted water ("M7") with water hardness of 2.5 mmol/L (= 250 mg/L as $CaCO_3$). pH values in the test media ranged from 7.6 to 8.0, dissolved oxygen concentrations were at least 8.1 mg/L. Water temperature ranged from 19 to 20 °C. Photoperiod was 16 hours light and 8 hours darkness. Test animals were fed on each working day with a defined amount of a mixture of green algae and of fish food suspension.
Dosage:	Prior to each test medium preparation, the test medium of the highest test concentration was freshly prepared by completely dissolving the test item at a concentration of 100 mg/L (intensive stirring for 10 minutes). In a series of dilution steps, this test medium was diluted with test water to prepare the test media of the lower test concentrations.
Analytics:	From the freshly prepared test media samples were taken from three preparation dates. Additionally two stability control samples (two and three days old, with and without food) were taken at the end of two treatment periods. The concentrations of lacosamide were analyzed by HPLC in the test media samples from the nominal concentrations of 32 and 100 mg/L, determined in the experiment as the NOEC and the LOEC.
Observations:	The daphnids were observed for mortality at least three times per week. Date of first offspring and number of offspring were recorded.

Endpoints/Statistics: The reproduction rate was calculated as the total number of living offspring produced per parent female surviving until the end of the test. The NOEC and the LOEC of the reproduction rate were statistically evaluated by testing the mean reproduction rate at the test concentrations for statistically significant differences to the control value by the multiple Williams-test.

Findings

The measured test item concentrations in the analyzed test media of nominal 32 and 100 mg/L varied in the range of 84 to 104% of the nominal values at the start and the end of the renewal periods. Under the conditions of the test with food and Daphnia, lacosamide was stable during the test medium renewal periods of two and three days. All reported biological results are related to the nominal concentrations of the test item.

Taking into account the survival rates and the reproduction rates of the test animals, the highest concentration of lacosamide tested without toxic effects after the exposure period of 21 days (21-day NOEC) was 32 mg/L.

The lowest concentration tested with toxic effects (21-day LOEC) was determined to be 100 mg/L due to the statistically significantly reduced mean reproduction rate of *Daphnia magna* at this test concentration.

With exception of the reported mortality and the reduced reproduction rates, no visible abnormalities were observed at the test animals during the test.

Summary of effects of lacosamide on *Daphnia magna* over 21 days of exposure:

	Control	Lacosamide (nominal concentration in mg/L)				
		1.0	3.2	10	32	100
Mortality after 21 days of exposure (%)	0	0	0	20	0	0
Mean reproduction rate in % of control	100	90.6	96.6	88.0	94.0	80.7 *

* statistically significantly lower than the control value, results of a Williams-test, one-sided, $\alpha = 0.05$

Conclusion

The **NOEC of lacosamide to *Daphnia magna* survival and reproduction was 32 mg/L**, the LOEC was 100 mg/L. **The NOEC/MEEC ratio for lacosamide in this chronic toxicity test by far exceeds a factor of 10** (>10'000; Appendix 11.2.4.3).

6.2.4 Summary on Assessment Factors in Environmental Effect Studies

The following table summarizes the test endpoints (EC_{50} or NOEC) derived from the environmental effect studies and compares the respective risk characterization ratios (i.e., ratio of (EC_{50} or NOEC and EIC or MEEC) with the assessment factors as required by *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998)*. The detailed calculations are given in Appendix 11.2.

Test	**Test Endpoint**	**Risk Characterization Ratio**	**Assessment Factor per Guideline**
Microbial respiration inhibition (OECD 209)	NOEC ≥1000 mg/L	NOEC/EIC >100'000	-
Tier 1 testing			
Algal growth inhibition (OECD 201)	EC_{50} >100 mg/L	EC_{50}/MEEC >10'000	1000
Higher tier testing (chronic toxicity studies to satisfy European Union requirements; not required per *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998)*)			
Fish early life stage (OECD 210)	NOEC ≥10 mg/L	NOEC/MEEC >1'000	10
Daphnia reprotox (OECD 211)	NOEC 32 mg/L	NOEC/MEEC >10'000	10

For estimation of the EEC (expected environmental concentration) in a first tier no depletion mechanisms, metabolism in humans or dilution was assumed to reduce the concentration in surface water. In this conservative approach, the maximum expected environmental concentration (MEEC) is thus considered to be equivalent to the EEC or EIC. In fact, when accounting for dilution of the sewage water when entering surface water the risk characterization ratios would be even higher.

6.3 Summary on Environmental Fate and Effect of Released Substances

After intake of lacosamide by patients for treatment of partial-onset seizures or diabetic neuropathic pain the substance is mainly excreted in the human urine. Besides unchanged lacosamide (approximately 40% of applied dose) the major metabolite (O-desmethyl lacosamide) and a polar fraction were found in human urine exceeding 10% of applied dose. The O-desmethyl metabolite (SPM 12809) has no known pharmacological activity. These substances may reach the aquatic environment (surface water) by transport via sewage and sewage works (POTWs) (Section 6.1.1).

In the aquatic environment once entered lacosamide is mainly present in the aqueous phase. Concluding from its physicochemical propertied (Section 6.1.2.7) such as high water solubility and low octanol/water coefficient (log Kow 0.25) no relevant partitioning into sewage sludge or sediment is expected. Although not required, this is confirmed by adsorption / desorption experiments showing low adsorption to the soils and the river sediment tested (mean Koc of 9 mL/g). A similar behavior is assumed for the major urine metabolites for which chemical structures and HPLC retention times indicate to be more polar thus to have a comparable or higher water solubility than the parent molecule. In conclusion, only the parent compound, i.e. the active moiety lacosamide, was studied in this EA as the substance relevant for the environmental risk assessment.

Exposure of the terrestrial and atmospheric compartment to lacosamide or its metabolites is expected to be insignificant (Section 6.1.5.2 and Section 6.1.5.3).

Forced degradation studies with lacosamide indicate that abiotic processes like hydrolysis or photolysis do not contribute significantly to the dissipation of lacosamide from the aquatic environmental compartment (Section 6.1.3.1). In a ready biodegradability test lacosamide was not readily degraded to carbon dioxide under the given stringent test conditions (Section 6.1.3.2). However, it is assumed that the compound is degraded to some extent under more realistic test conditions in the aquatic environment. For the present EA, in a conservative approach, it was assumed that the compound and its major urine metabolites are stable in surface water once they have entered the aquatic environment.

Testing on microbial inhibition was done in an activated sludge respiration inhibition test. Due to the absence of effects up to the highest concentration tested (1000 mg/L) no adverse effects on microbial degradation processes are expected in wastewater treatment facilities. The 3-hour NOEC (EC_{15}) exceeds by far (>100'000x) the EIC (environmental introduction concentration) estimated at the point of entry of lacosamide into POTWs via sewage (Appendix 11.2.4.1).

Based on the low potential for bioconcentration (log Kow < 3.5; Section 6.1.2.7) and the overall assessment of lacosamide's environmental fate indicating exposure mainly of the aqueous phase of the aquatic compartment (Section 6.1.5), tier 1 acute toxicity testing in one aquatic species is appropriate per *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998).* One suitable test proposed is an algal species bioassay.

Lacosamide had no inhibitory effect on the growth of the green algal species *Scenedesmus subspicatus* during the exposure period of 72 hours at the test concentration of nominal

100 mg/L (highest concentration tested without toxic effects after the exposure period of 72 hours) and there were no sublethal effects observed at any dose tested. The 72-hour EC_{50} was determined to be >100 mg/L. Comparison with the MEEC for the aquatic environment resulted in an EC_{50}/MEEC ratio clearly exceeding a factor of 1000 for tier 1 testing (>10'000; Appendix 11.2.4.2). The high margin of safety indicates that no adverse effects on the aquatic community are to be expected after entry of lacosamide into surface waters via sewage and POTWs and that no higher tier testing (tier 2 or 3 testing) is required per *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July, 1998).*

Nethertheless two chronic toxicity studies, an early life stage toxicity test in zebra fish and a reproduction test in daphnids, were performed to satisfy European Union requirements. The results of these tests are very reassuring in that no adverse effects of lacosamide on the aquatic community are to be expected: the NOEC/MEEC ratio for lacosamide in the early life stage test in zebra fish by far exceeds a factor of 10 for chronic toxicity testing (>1'000; Appendix 11.2.4.3). Similarly, the NOEC/MEEC ratio for lacosamide on survival and reproduction of *Daphnia magna* by far exceeds a factor of 10 for chronic toxicity testing (>10'000; Appendix 11.2.4.3).

Although ecotoxicological data for the major urine metabolites are not available their potential risk to aquatic organisms are covered by the high margin of safety determined for lacosamide. Even if the metabolites will exhibit a 10-times higher ecotoxicity than lacosamide, which is not expected due to absence of any known pharmacological activity, an assessment factor of >1000 could be applied on this theoretical endpoint without exceeding the calculated MEEC based on active moiety. Considering that the metabolites only account for approximately 20% and 30% of the dose in human excretions the margin of safety would be even higher.

7 MITIGATION MEASURES

No potential adverse environmental effects have been identified to be associated with the proposed action. Therefore, no mitigation measures are needed.

8 ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental effects have been identified to be associated with the proposed action. Therefore, no alternative course of action is needed.

9 LIST OF PREPARERS

Dr. Enrico Kiefer, Head of Product Safety, RCC Ltd. (Consultant)

- PhD in Medical Zoology.
- Master in Biology, optional subject chemistry (University of Basle).
- Project Leader and Head of Product Safety at RCC Ltd., managing a team of product safety experts.
- More than 10 years' experience in assessing the environmental safety of crop protection and biocidal products with the agro-chemical industry, including 6 years in management position (Global Head of Environmental Safety Assessments and Contracting with Syngenta Crop Protection AG).
- Experience in scientific monitoring of ecochemistry studies, preparation of environmental assessments for pesticides, biocides, veterinary and human drugs.
- Former member of the OECD Expert Group on Aquatic Risk Indicators, and of the ECPA Environmental Expert Group.

Dr. Niels Krebsfänger, Senior Toxicologist, SCHWARZ BIOSCIENCES GmbH (Project Toxicologist)

- Dr. rer. nat. and diploma in biochemistry.
- Diplomate of the American Board of Toxicology (D.A.B.T.), certified toxicologist by the Federation of European Toxicologist & European Societies of Toxicology (EUROTOX Registered Toxicologist) and Gesellschaft für Toxikologie in der Deutschen Gesellschaft für experimentelle und klinische Pharmakologie und Toxikologie (Fachtoxikologe DGPT).
- More than 9 years training and experience in general toxicology in academia, contract research and pharmaceutical industry.
- Member of several (inter)national toxicological societies and working groups (DGPT, BTS, EUROTOX, A.B.T, ISSX).

10 REFERENCES

Research Reports Cited in the Present EA Expert Report on Lacosamide

Report No.	Location in CTD	Title
A22173	4.2.3.7.7	SPM 927: Ready biodegradability in a CO_2 evolution (modified Sturm) test. Itingen, Switzerland: RCC Ltd.; January 2006
A22184	4.2.3.7.7	SPM 927: Toxicity to *Scenedesmus subspicatus* in a 72-hour algal growth inhibition test. Itingen, Switzerland: RCC Ltd.; December 2005
A22206	4.2.3.7.7	SPM 927: Adsorption/desorption of [^{14}C]-SPM 927 on soils. Itingen, Switzerland: RCC Ltd.; March 2006
A27033	4.2.3.7.7	SPM 927: Toxicity to activated sludge in a respiration inhibition test. Itingen, Switzerland: RCC Ltd.; December 2005
A45180	4.2.3.7.7	SPM 927: Toxic effects to Zebra fish (Brachydanio rerio) in an early-life stage toxicity test (OECD 210). Itingen, Switzerland: RCC Ltd.; August 2006
A45202	4.2.3.7.7	SPM 927: Effect on survival and reproduction of Daphnia magna in a semi-static test over three weeks (OECD 211). Itingen, Switzerland: RCC Ltd.; August 2006

Further References

The EA was prepared following the *'Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application' (FDA, CMC 6, Rev 1, July 1998)*

11 APPENDICES

11.1 Non-confidential Information

11.1.1 Data Summary Table

Data Summary Table on Endpoints for Lacosamide

Test	Endpoint	CTD Module / Report No. (Location in CTD)
Physical/Chemical Characterization		
Water solubility (25°C) in phosphate buffer, pH 4.5 in phosphate buffer, pH 7.5 in pure water	 Modification 1 : 28.4 mg/mL Modification 2 : 28.9 mg/mL Modification 1 : 20.1 mg/mL Modification 2 : 20.8 mg/mL Modification 1 : 30.2 mg/mL Modification 2 : 30.8 mg/mL	3.2.S.1.3 and 3.2.S.3.1
Log Kow (n-octanol / water partition coefficient) (OECD 107, shake flask method)	0.25 (mean, n=6)	3.2.S.1.3 and 3.2.S.3.1
Koc (adsorption / desorption coefficient normalized for organic carbon content of test soils) (OECD 106)	9 mL/g (adsorption) 12 mL/g (desorption)	A22206 (4.2.3.7.7)
Dissociation constant	No dissociation at environmentally relevant pH (pKa outside pH range of 1.5 to 12).	3.2.S.1.3 and 3.2.S.3.1
Vapour pressure at 25° C	$9.3 * 10^{-5}$ Pa (calculated)	3.2.S.1.3
Henry's Law Constant at 25°C	$1.14 * 10^{-11}$ atm*m^3/mol (calculated)	3.2.S.1.3

Continued on next page

Data Summary Table on Endpoints for Lacosamide (Continued)

Test	Endpoint	CTD Section / Report No.
Environmental Depletion Mechanisms		
Hydrolysis	Hydrolytically stable at environmentally relevant conditions, hydrolysis $T_{½} > 24$ hours	3.2.S.7.3
Photolysis	No significant degradation in solid state or aqueous solution after irradiation with 20'000 kJ/m^2 (1.2 million lux hours) or 100.000 kJ/m^2 (6 million lux hours) in aqueous solution.	3.2.S.7.3
Aerobic biodegradation (OECD 301 B, modified Sturm test)	Not readily biodegradable to carbon dioxide within 28 days under the stringent test conditions	A22173 (4.2.3.7.7)
Environmental Effects		
Inhibition of microbial respiration rate of activated sludge (OECD 209)	3-hour $EC_{50} > 1000$ mg/L 3-hour NOEC (EC_{15}) ≥ 1000 mg/L	A27033 (4.2.3.7.7)
Effects on algal growth of green alga *Scenedesmus subspicatus* (OECD 201)	72-hour ErC50/EbC50 > 100 mg/L	A22184 (4.2.3.7.7)
Fish Early Life Stage (OECD 210)	NOEC for all parameters tested ≥ 10 mg/L	A45180 (4.2.3.7.7)
Daphnia Reproduction (OECD 211)	21-day NOEC was 32 mg/L on survival and reproduction rates of *Daphnia magna*	A45202 (4.2.3.7.7)

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/s/

Jon E. Clark
5/15/2008 02:08:31 PM

Moheb Nasr
5/15/2008 04:18:41 PM

ENVIRONMENTAL ASSESSMENT

and

FINDING OF NO SIGNIFICANT IMPACT

for

Lacosamide
10 mg/ml solution for infusion

NDA 22-254

Food and Drug Administration
Center for Drug Evaluation and Research

Date Completed: May 11, 2008

[redacted]

FINDING OF NO SIGNIFICANT IMPACT

NDA 22-254

Lacosamide
10 mg/ml solution for infusion

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 impact on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of its new drug application for Lacosamide, 10 mg/ml solution for infusion, Schwarz Bioscience, Inc. prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product.

Lacosamide is intended for use as a drug for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy, and management of neuropathic pain associated with diabetic peripheral neuropathy.

Lacosamide may enter the environment from patient use and disposal. It is expected to enter into the aquatic environment. Data indicate that the compound is unlikely to enter the terrestrial and atmospheric environments. The toxicity of lacosamide to aquatic organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at expected environmental concentrations.

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

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

PREPARED BY:

Ruth Ganunis, Ph.D.
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Director, Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment:

Environmental Assessment dated June, 2007
Appended Electronic Signature Page

ENVIRONMENTAL ASSESSMENT (EA)

OF LACOSAMIDE

EXPERT REPORT

TABLE OF CONTENTS

SIGNATURES

The present Environmental Assessment Expert Report was prepared by:

Environmental Expert:

June 26, 2007 .....

Date Dr. Enrico Kiefer
RCC Ltd.

Sponsor's Representative:

June 28, 2007 .....

Date Dr. Niels Krebsfänger, D.A.B.T.
SCHWARZ BIOSCIENCES GmbH

1 DATE

Date of EA preparation: **June, 2007**

Date of subsequent amendment(s): --

2 NAME OF APPLICANT OR PETITIONER

SCHWARZ BIOSCIENCES, Inc.

3 ADDRESS

P.O. Box 110167

Research Triangle Park, NC 27709

8010 Arco Corporate, Suite 100

Raleigh, NC 27617

USA

4 DESCRIPTION OF PROPOSED ACTION

4.1 Requested Approval

Schwarz Biosciences, Inc. has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for lacosamide tablets (50 mg, 100 mg, 150 mg, 200 mg, 250 mg, and 300 mg) packaged in HDPE bottles and PVC/PVDC aluminum blisters, lacosamide 10 mg/ml solution for infusion packaged in clear glass vials with rubber stopper and aluminum cap, and lacosamide 15 mg/ml syrup packaged in brown glass or PET bottles. An EA has been submitted pursuant to 21 CFR part 25.

4.2 Need for Action

Lacosamide is intended for use as drug for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy, and management of neuropathic pain associated with diabetic peripheral neuropathy.

4.3 Locations of Use

The locations of use will typically be hospitals, clinics and/or patients in their homes. The intravenous solution for infusion may also be used in emergency settings.

4.4 Disposal Sites

At U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures in accordance with local requirements. In the home, 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, although minimal quantities of the unused drug could be disposed of in the sewer system.

5 IDENTIFICATION OF SUBSTANCE THAT IS THE SUBJECT OF THE PROPOSED ACTION

5.1 Nomenclature

5.1.1 Established Name (INN/USAN/Laboratory Codes and Previous Names)

International Nonproprietary Name (INN):
Lacosamide

United States Adopted Name (USAN):
Lacosamide

Laboratory Codes and Previous Names:
SPM 927, ADD 234037, harkoseride

5.1.2 Brand/Proprietary Name/Trade Name

Not yet available.

5.1.3 Chemical Names

Chemical Abstracts (CA) Index Name:
Propanamide, 2-(acetylamino)-3-methoxy-N-(phenyl methyl)-, (2R)-

Systematic Chemical Name (IUPAC):
(R)-2-Acetamido-N-benzyl-3-methoxypropionamide

5.2 Chemical Abstracts Service (CAS) Registration Number

175481-36-4

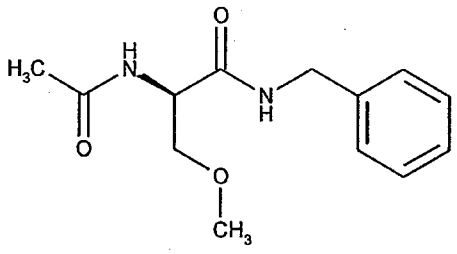
5.3 Molecular Formula

$C_{13}H_{18}N_2O_3$

5.4 Molecular Weight

250.3

5.5 Structural Formula



Lacosamide is the single (R)-enantiomer.

APPEARS THIS WAY
ON ORIGINAL

6 ENVIRONMENTAL ISSUES

6.1 Environmental Fate of Released Substances

6.1.1 Identification of Substances of Interest

Human metabolism and excretion of lacosamide is described in CTD Module 2.7.2.3.3 and CTD Module 2.7.2.3.4, respectively, and briefly summarized below.

After oral and intravenous administration of 100 mg [^{14}C]-lacosamide (45 µCi) in healthy subjects, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the feces. The major compounds excreted were unchanged lacosamide (SPM 927, approximately 40% of the dose) and its O-desmethyl-metabolite (SPM 12809, approximately 30%). A polar fraction accounted for approximately 20%. Small amounts (0.5 to 2%) of further metabolites were found in the urine: the p-hydroxy-, the O-desmethyl-p-hydroxy-, O-desmethyl-m-hydroxy-, and the desacetyl derivatives of lacosamide. In addition, a N-carbamoyl-O-ß-D-glucuronide of the desacetyl metabolite has been identified. In plasma the O-desmethyl metabolite SPM 12809 represents approximately 10% of the parent compound. In conclusion the major human metabolite is SPM 12809. This metabolite has no known pharmacological activity.

Additional stereo-specific analysis of urine samples showed that there is no enantiomeric interconversion of lacosamide.

With regard to the structure of the polar fraction, the analytical results do not allow evident proposals for exact chemical structures, though they indicate small polar molecules close to the R-serine backbone. This seems to be most probable since larger molecules could not be observed in the respective MS-spectra and the expressed polar chromatographic behavior indicates loss of lipophilic structural elements.

The findings of the metabolism/excretion study show that excretion of unchanged lacosamide and the metabolites formed mainly occurs via urine (approximately 95% of applied dose). Thus, the substances of interest for the environmental assessment are besides unchanged lacosamide the major O-desmethyl metabolite SPM 12809 and a polar fraction, which potentially can reach surface waters (aquatic environment) via sewage systems. These compounds account for approximately 90% of the dose. The major metabolite (O-desmethyl metabolite, SPM 12809) in humans has no known pharmacological activity. All other metabolites found in urine were below 2% and are like the polar fraction assumed to be also pharmacologically not active. Physico-chemical data on the major human metabolite SPM 12809 (O-desmethyl lacosamide) are not available. But concluding from its chemical structure (i.e., due to de-masking of a polar hydroxy group) and the retention times in HPLC-runs the substance is considered more polar than lacosamide, and therefore expected to have a comparable or higher water solubility than the parent compound. Thus, only the parent compound, i.e. the active moiety lacosamide, was studied in this EA as the substance relevant for the environmental risk assessment.

6.1.2 Physical and Chemical Characterization

The table in Appendix 11.1.1 lists the physico-chemical properties of lacosamide (see also CTD Module 3.2.S.1.3 and CTD Module 3.2.S.3.1).

6.1.2.1 Polymorphism

Investigations on polymorphism of lacosamide have shown that the drug substance can be present in more than one crystalline structure. Four different crystalline structures and one amorphous form were identified (CTD Module 3.2.S.1.3). Two of the crystalline structures (modifications 1 and 2) are routinely formed in the regular synthesis of lacosamide drug substance and only these modifications are existent in lacosamide drug substance batches. Modification 3 is a crystalline, metastable modification that appears only by crystallization from methylene chloride at room temperature. The fourth modification (modification 4) is stable only up to -120°C and converts to modification 1 above -120°C. The amorphous state is widely unstable under normal laboratory conditions and converts rapidly to a crystalline modification.

6.1.2.2 Water Solubility

Solubility measurements were performed in aqueous solutions with modification 1 and 2 at 37°C and 25°C. The water solubility for both modifications was comparable, ranging from 28.4 to 28.9 g/L in phosphate buffered aqueous solutions at pH 4.5 at 25° C. In phosphate buffered solutions of pH 7.5 solubilities were slightly lower ranging from 20.1 to 20.8 g/L at 25°C. In pure water the measured solubilities were in the range of 30.2 to 30.8 g/L
(CTD Module 3.2.S.1.3 and CTD Module 3.2.S.3.1).

6.1.2.3 Octanol / Water Partition Coefficient (log Kow)

The n-octanol / water partition coefficient was determined at 20°C using the shake flask method (CTD Module 3.2.S.1.3 and CTD Module 3.2.S.3.1). The concentration of lacosamide in the octanol and water phase was determined by HPLC. Although not explicitly stated in the report the experiment followed the testing principles of OECD test guideline 107 (shake flask method). The partition coefficient (log Kow) was determined to be 0.25 (mean value of 6 determinations from different n-octanol / water ratios).

6.1.2.4 Adsorption / Desorption Coefficient (Koc)

Since log Kow was determined to be less than 3 (Section 6.1.2.3) no further study on adsorption / desorption properties is required as per the *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July, 1998)*. However, the adsorption / desorption coefficient (Koc) has been determined to satisfy European Union requirements and is reported below.

The adsorption / desorption behavior of [^{14}C]- lacosamide was investigated on four soils (soil I, II, III and V) and one river sediment (soil IV) differing in their organic matter content, cation exchange capacity, pH and particle size (CTD Table 2.6.7.17, A22206). The test was done under GLP following the batch equilibrium method according to OECD test guideline 106. In preliminary tests for determination of the soil to solution ratios and the equilibration time some instability of lacosamide was observed in the supernatants of the soil I and II after 48 hours of adsorption. In order to minimize degradation the soils were sterilized by γ-irradiation (soil I, II, III and V) for the screening tests. Sterilization of the sediment was considered not necessary since a pre-test under non-GLP conditions showed the stability of the compound in this test system.

The screening tests were conducted with all soils/sediment at a concentration of 0.05 mg/L and at a soil/solution ratio of 1:1. After 2, 5, and 24 hours of shaking, the amount adsorbed was determined for all soils/sediment. After 24 hours of incubation 11.3%, 20.4%, 11.4%, 10.9% and 12.2% of the amount applied was adsorbed for soils I to V, respectively.

The desorption was subsequently performed after the adsorption step. The test item concentration in the supernatant was determined for all soils/sediment after 2, 5, 24 and 48 hours. The desorption equilibrium was reached very fast (i.e. within not more than five hours).

HPLC analyses of the supernatants of adsorption and desorption experiments showed, that lacosamide remained stable under the test conditions (i.e. using soils sterilized by γ-irradiation).

The following adsorption/desorption coefficients normalized for organic carbon content of the soils/sediment were determined (K_{OC}):

Soil	Soil I (loam)	Soil II (clay loam)	Soil III (silty clay loam)	Soil IV (sandy loam) [River sediment]	Soil V (silt loam)	Mean values
K_{OC} (mL/g)	10	6	5	16	7	9
$K_{des,OC}$ (mL/g)	16	9	5	20	10	12

A mean adsorption K_{OC} of 9 mL/g and a mean desorption $K_{des,OC}$ of 12 mL/g was calculated. The calculated $K_{des,OC}$ values were slightly higher than those obtained for the adsorption isotherms, indicating reversibility of the adsorption process. Only a small part of radioactivity (less than 4%) could not be extracted with organic solvents and therefore, remained bound to the soil.

6.1.2.5 Dissociation Constant (pKa)

The dissociation constant in water was determined by potentiometric (conductometric) titration (CTD Module 3.2.S.1.3 and CTD Module 3.2.S.3.1). No pKa value could be determined for lacosamide drug substance within the measured pH range of 1.5 to 12. It is concluded that there is no relevant dissociation of SPM 927 at pH relevant in the environment.

6.1.2.6 Vapor Pressure and Henry's Law Constant

The vapor pressure of lacosamide was calculated to be 9.3×10^{-5} Pa at 25°C based on an estimated boiling point of 334°C, and using the Modified Watson Correlation. From this calculated vapor pressure and based on the lowest reported solubility of 20.1 g/L a Henry's Law Constant of $1.14 * 10^{-11}$ atm*m^3/mol was estimated for aqueous phosphate buffered solution at pH 7.5 (3.2.S.1.3).

6.1.2.7 Conclusion

The physico-chemical characterization of lacosamide (water solubility of > 20 g/L, Henry's Law Constant of $1.14 * 10^{-11}$ atm*m^3/mol, log Kow of 0.25, no relevant dissociation at environmentally relevant pH) indicate the substance to be predominantly present in the water phase in undissociated form in the aquatic environment. This is further supported by a mean K_{OC} of 9 mL/g indicating a low potential of lacosamide to bind to the organic fraction of soils, sediments and biosolids (i.e., sludge).

The potential for bioconcentration is considered to be low (log Kow < 3.5), and tier 1 acute toxicity testing in one aquatic species should be performed, i.e. no further testing on bioconcentration, terrestrial species or chronic toxicity testing is triggered according to the *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July, 1998)*.

Physico-chemical data on the major human metabolite SPM 12809 (O-desmethyl lacosamide) are not available. However, concluding from its chemical structure (i.e., due to de-masking of a polar hydroxy group) and the retention times in HPLC-runs the substance is considered more polar than lacosamide, and therefore expected to have a comparable or higher water solubility than the parent compound.

6.1.3 Environmental Depletion Mechanisms

6.1.3.1 Forced Degradation Studies

Forced degradation studies with lacosamide were performed to evaluate the stability of the substance under various stress conditions (CTD Module 3.2.S.7.3).

Temperature and Humidity

Lacosamide was found to be very stable at elevated temperatures and high humidity. Open storage of lacosamide for 71 days at 120°C showed only little degradation of the substance. Degradation products observed at the end of the experiment accounted in total for ≤ 0.3%. Open and closed storage under accelerated conditions (40°C and 75% relative humidity) for 12 weeks showed no significant degradation of the substance.

Photolysis

In photostability tests lacosamide proved to be stable in solid state and in aqueous solution after irradiation with 20'000 kJ/m^2 (1.2 million lux hours) in a SUN-TEST apparatus. Even after irradiation with 100.000 kJ/m^2 (6 million lux hours) in aqueous solution in quartz vials lacosamide accounted for 99.95 % of the initial concentration.

Hydrolysis

In aqueous solutions at moderate acidic (pH 3) and at neutral conditions (pH 7) a decrease of lacosamide of 2-5% was observed after 4 weeks storage at 60°C. Under strong acidic (pH 1) and alkaline conditions (pH 10) at a temperature of 60°C the substance rapidly decomposed (in 0.1 N NaOH quantitative degradation was observed after 24h). Moderate degradation was reported after addition of 3% hydrogen peroxide to aqueous solutions of pH 3, pH 7 and pH 10. After 24 hours storage at room temperature (25°C) under oxidizing conditions a decrease of 2-6% of lacosamide was reported.

Conclusion

The results of the forced degradation studies indicate lacosamide to be stable under environmental relevant temperature and pH conditions. Abiotic degradation processes like hydrolysis, photolysis and thermal decomposition are not expected to contribute significantly to rapid dissipation of lacosamide from aquatic and terrestrial compartments after entry into the compartment.

6.1.3.2 Ready Biodegradability

Lacosamide was investigated for its ready biodegradability in a 28-day CO_2 evolution test (Modified Sturm test, OECD Guideline for Testing of Chemicals, No. 301 B (1992)). The test was conducted under GLP (CTD Table 2.6.7.17, A22173).

In this test evolution of CO_2 within 28 days was measured after adding lacosamide at a concentration of 25 mg/L (equivalent to 15.6 mg TOC/L) to the test medium including as an inoculum's activated sludge from a wastewater treatment plant. The toxicity of lacosamide to the

inoculum was tested before in a microbial respiration inhibition test (CTD Table 2.6.7.17, A27033; see Section 6.2.1). Lacosamide was found to have no inhibitory effect on the respiration rate of activated sludge after 3 hours incubation up to 1000 mg/L (highest concentration tested).

In the test on ready biodegradability the carbon dioxide formed after addition of lacosamide to the inoculated test medium was trapped in adsorber flasks containing NaOH and sampled at different time intervals up to 28 days. The samples were analyzed for inorganic carbon (IC) using a TOC analyzer.

The CO_2 production of the test item lacosamide in the test media was 3-4% at the end of the test (day 28) and thus only slightly higher than in the inoculum controls. According to the respective OECD Guidelines, based on ultimate biodegradation (i.e. CO_2 evolution), lacosamide has to be considered to be not readily biodegradable under the test conditions.

In comparison, the reference item (sodium benzoate) was degraded to an average extent of 76% by exposure Day 14 in procedure controls, confirming the validity of the test conditions (>60% degradation by Day 14). By the end of the test the reference substance was completely degraded. In controls containing lacosamide and test medium de-activated by addition of mercury dichloride, no degradation was noted at the end of the 28-day exposure period.

However, the ready biodegradability test measuring as an endpoint formation of CO_2 does not give information on the inherent biodegradability of test substances when the test substance is not extensively degraded to carbon dioxide within the test period.

6.1.3.3 Conclusion

Since no significant degradation processes were identified so far no rapid depletion due to abiotic or biotic degradation was assumed as a worst-case for assessment of the fate of lacosamide in the aquatic environment.

6.1.4 Environmental Concentrations

6.1.4.1 Expected Introduction Concentration (EIC)

The expected introduction concentration (EIC) of lacosamide (SPM 927) into the aquatic environment was calculated according to the equation given in the *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications, Section III.A.2 (July, 1998)*:

EIC-Aquatic (ppb) = A x B x C x D

Where

A= kg/year produced for direct use (as active moiety) in any of the next 5 five years (i.e. based on sales forecast for years 2008 to 2012; Appendix 11.2.1)

B= 1/litres per day entering POTWs

(1.214 x 10^{11} liters per day entering publicly owned treatment works (POTWs, Source: 1996 Needs Survey, Report to Congress)

C= year/365

D= 10^{9} µg/kg (conversion factor)

For calculation of the EIC for lacosamide it was assumed that

- All quantities of lacosamide in drug products produced in a year for treatment of partial-onset seizures and diabetic neuropathic pain are used and enter the POTW system.
- Drug product usage occurs throughout the United States in proportion to the population and amount of wastewater generated.
- There is no metabolism (i.e. the active moiety corresponds to unchanged lacosamide).
- There is no significant environmental depletion in the waste treatment process.

Under these conservative assumptions the EIC exceeds 1 ppb (µg/L) at the point of entry into the aquatic environment (Appendix 11.2.2). Accordingly, the drug application is subject for preparation of an EA.

6.1.4.2 Expected Environmental Concentration (EEC, MEEC)

For deriving the expected environmental concentration (EEC) for the aquatic compartment no dilution or degradation was assumed as a conservative first tier estimate for lacosamide entering surface waters after passage of POTWs. **Thus, the maximum expected environmental concentration (MEEC) was set to be equivalent to the EEC or EIC in a conservative approach (Appendix 11.2.3).**

6.1.5 Summary on Environmental Fate of Released Substances

6.1.5.1 Aquatic Compartment

The expected introduction concentration (EIC) of lacosamide into the aquatic environment was calculated based on the fifth-year marketing estimate assuming all quantities produced in a year are used and enter POTWs as active moiety. Under this conservative assumption the EIC exceeds 1 ppb (µg/L) at the point of entry into the aquatic environment and the drug application is subject for preparation of an EA. For estimation of the EEC (expected environmental concentration) in a first tier no depletion mechanisms, metabolism in humans or dilution was assumed to reduce the concentration in water. In this conservative approach, the maximum expected environmental concentration (MEEC) is thus considered to be equivalent to the EEC or EIC.

After intake of lacosamide by patients for treatment of partial-onset seizures or diabetic neuropathic pain the substance is mainly excreted in the human urine. Besides unchanged lacosamide (approximately 40% of applied dose) the major metabolite (O-desmethyl lacosamide) and a polar fraction were found in human urine exceeding 10% of applied dose. The O-desmethyl metabolite (SPM 12809) has no known pharmacological activity. These substances may reach the aquatic environment (surface water) by transport via sewage and sewage works (POTWs).

In the aquatic environment once entered lacosamide is mainly present in the aqueous phase. Concluding from its high water solubility and low octanol/water coefficient (log Kow 0.25) no relevant partitioning into sewage sludge or sediment is expected. Although not required, this is confirmed by adsorption / desorption experiments showing low adsorption to the soils and the river sediment tested (mean Koc of 9 mL/g). A similar behavior is assumed for the major urine metabolites for which chemical structures and HPLC retention times indicate to be more polar thus to have a comparable or higher water solubility than the parent molecule.

Forced degradation studies with lacosamide indicate that abiotic processes like hydrolysis or photolysis do not contribute significantly to the depletion of lacosamide from the aquatic environmental compartment. In a ready biodegradability test lacosamide was not readily degraded to carbon dioxide under the given stringent test conditions. However, it is assumed that the compound is degraded to some extent under more realistic test conditions in the aquatic environment. For the present EA, in a conservative approach, it was assumed that the compound and its major urine metabolites are stable in surface water once they have entered the aquatic environment.

6.1.5.2 Terrestrial Compartment

Exposure of the terrestrial compartment is expected to be insignificant if the usual recommendations for disposal of unused drugs and empty packages are followed. Since lacosamide and its major urine metabolites are predominantly present in the aqueous phase partitioning into sludge of wastewater treatment plants will be negligible. No relevant exposure

is therefore expected from spreading of sludge on agricultural land for fertilization. Due to the low Kow of 0.25 and mean Koc of 9 mL/g no further testing on fate and effects on the terrestrial environment is indicated.

6.1.5.3 Atmospheric Compartment

Substantive volatilization from the aquatic or terrestrial environment to the atmospheric environment is not expected for lacosamide and its major urine metabolites. Due to the high water solubility of lacosamide and its low calculated vapor pressure and Henry's Law Constant there will be no substantive partitioning from the aquatic to the atmospheric compartment. Further, medical indications of lacosamide do not include applications as aerosol spray or medical gases and therefore exposure of air is considered to be not relevant.

6.2 Environmental Effects of Released Substances

6.2.1 Microbial Inhibition Testing

The inhibitory effect of lacosamide on the respiration rate of aerobic wastewater microorganisms of activated sludge was investigated in a 3-hour respiration inhibition test according to OECD Guideline for Testing of Chemicals, No. 209. The test was done under GLP (CTD Table 2.6.7.17, A27033).

Test Design

Test species:	Aerobic activated sludge collected from a wastewater treatment plant (ARA Ergolz II, Füllinsdorf, Switzerland) treating mainly domestic wastewater.
Test conditions:	2000 mL glass beakers; test medium: synthetic wastewater (feed solution), activated sludge inoculum, and test item at a final volume of 500 mL; suspended solid concentration: 1.2 g dry material/L; aerated for 3 hours at 20°C; pH 7.6 – 8.5
Test concentrations:	Nominal concentrations of lacosamide of 10, 32, 100, 320, and 1000 mg/L were tested. In addition, two non-treated negative controls and three different concentrations of the reference item 3,5-dichlorophenol (5, 16 and 50 mg/L) were tested in parallel. The results of these treatments confirmed the suitability of the activated sludge and the method used.
Test endpoints:	Assessment of the inhibitory effect of the test item on the oxygen consumption rate of aerobic micro-organisms (activated sludge) after short-term exposure of 3 hours. The median effective concentration (3-hour EC_{50}) for the reference item (3,5-dichlorophenol) was calculated by Probit analysis.

Findings

Up to and including the concentration of 1000 mg/L the test item had no inhibitory effect (<15%) on the respiration rate of activated sludge after the incubation period of three hours (Table). Thus, the 3-hour NOEC (EC_{15}) of lacosamide to activated sludge microorganisms was at least 1000 mg/L. This value might even be higher, but concentrations in excess of 1000 mg/L were not tested. The 3-hour EC_{20}, EC_{50} and EC_{80} could not be calculated, but were clearly higher than 1000 mg/L.

The EC_{50} of the reference item 3,5-dichlorophenol (13 mg/L) was within the range of 5 to 30 mg/L as required by the OECD Guideline 209 confirming the suitability of the test system.

Influence of Lacosamide on Oxygen Consumption of Activated Sludge

Test chemical	Nominal concentration of test chemical (mg/L)	Oxygen consumption rate (mg O_2/L min^{-1})	Inhibition (%)
Control	0	1.155	
Control	0	1.218	
Mean		1.186	
Deviation (%)		5.5	
SPM 927	10	1.184	0.2
SPM 927	32	1.253	-5.7
SPM 927	100	1.232	-3.9
SPM 927	320	1.246	-5.0
SPM 927	1000	1.204	-1.5

Conclusion

The 3-hour EC_{50} of lacosamide in the activated sludge respiration inhibition test was >1000 mg/L. **The 3-hour NOEC (EC_{15}) was ≥1000 mg/L. The 3-hour NOEC exceeds by far (>100'000x) the EIC** (environmental introduction concentration) estimated at the point of entry of lacosamide into POTWs via sewage (Appendix 11.2.4.1).

6.2.2 Effects on Aquatic Organisms: Tier 1 Testing

Based on the low potential for bioconcentration (log Kow < 3.5; Section 6.1.2.7) and the overall assessment of lacosamide's environmental fate indicating exposure mainly of the aqueous phase of the aquatic compartment (Section 6.1.5), tier 1 acute toxicity testing in one aquatic species is appropriate per *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998).* One suitable test proposed is an algal species bioassay.

6.2.2.1 Effects on growth of *Scenedesmus subspicatus*

The influence of the test item lacosamide on the growth of the green algal species *Scenedesmus subspicatus* CHODAT was investigated in a 72-hour static test according to OECD Guideline No. 201, 1984. The test was conducted under GLP (CTD Table 2.6.7.17, A22184).

Test Design

Test species:	Green alga *Scenedesmus subspicatus* CHODAT (Strain No. 86.81); Source: SAG (Culture Collection of Algae) Göttingen, Germany.
Test design:	1 concentration with three replicates and a blank test medium control group with 6 replicates were tested under static conditions for 72 hours.
Test concentration:	nominal 100 mg lacosamide/L, a limit test was done based on the results of a range finder test.
Inoculum at test start:	Nominal 1 x 10^4 cells/mL from a 4-day old exponentially growing pre-culture.
Test conditions:	Volumes of 15 mL algal suspension for each replicate were continuously stirred by magnetic stirrers in 50 mL Erlenmeyer flasks. The flasks were covered with glass dishes, incubated in a temperature controlled water bath at a temperature of 22 °C, and continuously illuminated at a measured light intensity of about 7400 Lux (mean value). The pH at 0 and 72 hours was 8.2 and 8.5 for both control and treated sample.
Dosage:	A single test item concentration of nominal 100 mg/L was tested. Additionally, a control was tested in parallel (test water without addition of the test item). The test medium of nominal 100 mg/L was prepared by dissolving 69.8 mg of test item completely in 700 mL of test water using ultrasonic treatment and intense stirring (5 minutes each) at room temperature. The test concentration was based on the results of a range-finding test (without GLP). Concentrations in excess of nominal 100 mg/L have not been tested in compliance with EU Commission Directive 92/69/EEC (limit test).
Analytics:	Concentrations of the test substance were measured by means of HPLC at test start and after 72 h.

Observations:	Algal cell densities in the samples were determined by counting with an electronic particle counter, at least two measurements per sample. In addition, shape and size of the algal cells was examined microscopically in samples taken from the control and the single test concentration after 72 hours exposure.
Endpoints/Statistics:	Inhibition of algal growth was determined from the mean values of counted algal cell densities. The test concentrations corresponding to 10 and 50% inhibition of the algal biomass b (E_bC_{10}, E_bC_{50}), or of the growth rate r (E_rC_{10}, E_rC_{50}) could not be calculated due to the absence of a toxic effect of the test item. LOEC and NOEC were determined directly from the counted algal cell densities. The mean cell densities were tested on significant differences to the control values by the STUDENT-t-test ($\alpha = 0.05$, one sided smaller).

Findings

The analytically determined test item concentration in the analyzed test medium ranged from 91 to 93% of the nominal value. Consequently, the test item was stable during the test period of 72 hours under the conditions of the test, and the reported biological results are based on the nominal concentration of the test item.

The test item lacosamide clearly had no inhibitory effect on the growth of *Scenedesmus subspicatus* during the exposure period of 72 hours at the test concentration of 100 mg/L. The 72-hour NOEC (highest concentration tested without toxic effects after the exposure period of 72 hours) of lacosamide to *Scenedesmus subspicatus* was therefore determined to be at least 100 mg/L. This value might even be higher, but concentrations in excess of 100 mg/L have not been tested according to EU Commission Directive 92/69/EEC.

The 72-hour LOEC (lowest concentration tested with toxic effects after the exposure period of 72 hours) and the 72-hour EC_{10} and EC_{50} for the algal biomass b and growth rate r could not be quantified due to the absence of a toxic effect of lacosamide at the tested concentration. Accordingly, these parameters are clearly higher than 100 mg/L.

Upon microscopic examination there were no obvious effects on the shape and size of the algal cells growing in the test medium at the nominal concentration of 100 mg/L after 72 hours exposure.

Conclusion

The 72-hour EC_{10} and **EC_{50} are >100 mg/L** and there were no sublethal effects observed at any dose tested, i.e. the NOEC was ≥100 mg/L. **The EC_{50}/MEEC ratio for lacosamide in this tier 1 test clearly exceeds a factor of 1000** (>10'000; Appendix 11.2.4.2). Thus, no higher tier testing (tier 2 or 3 testing) is required per *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998)*.

6.2.3 Effects on Aquatic Organisms: Higher Tier Testing

Although higher tier testing (tier 2 or 3 testing) for lacosamide is not required per *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998)* as discussed in Section 6.1.2.7, Section 6.2.2 and Section 6.3, an early life stage toxicity test in zebra fish and a reproduction test in daphnids were performed to satisfy European Union requirements. Data from those supplementary chronic toxicity tests are presented in this section for information on the ecotoxicity data available on lacosamide.

6.2.3.1 Effects on Fish Early Life Stage

The toxicity of the test item lacosamide to zebra fish (*Brachydanio rerio*) was investigated in an early life stage toxicity test according to the OECD Guideline for Testing of Chemicals, No. 210, "Fish, Early-life Stage Toxicity Test", 1992. (CTD Table 2.6.7.17, A45180)

Test Design

Test species:	The study was performed with newly fertilized eggs from zebra fish, *Brachydanio rerio* (Hamilton-Buchanan 1822, Teleostei, Cyprinidae). The origin of the strain of zebra fish is West Aquarium GmbH, D-37431 Bad Lauterberg, Germany. In the laboratories of RCC a brood batch of at least 200 individuals of this strain was held.
Test design:	A flow through system was used for the exposure of the eggs, larvae and fish. Depending on the size of the fish, glass vessels up to 2.0 liter volume were used. Four replicates were used for each test concentration and the control. 60 freshly fertilized eggs were exposed to four replicates of each test concentration and the control (15 eggs per replicate). The test duration was 5 days post fertilization plus 30 days post-hatch, in total 35 days.
Test concentration:	Nominal 0.10, 0.32, 1.0, 3.2, and 10 mg lacosamide/L, in parallel with a control. Test concentrations were based on the results of a range finder test.
Test conditions:	The test was conducted in reconstituted water with water hardness of 1.25 mmol/L (= 125 mg/L) as $CaCO_3$ pH values in the test media ranged from 7.0 to 7.1, dissolved oxygen concentrations were at least 6.6 mg/L. Water temperature ranged from 25.6 to 26.4 °C. Photoperiod was 16 hours light and 8 hours darkness. Test animals were fed ad libitum each day with live rotifers, live nauplia of *Artemia salina* and/or commercial dry fish food.
Dosage:	In this flow-through test, the concentrations of the test item in the test media were maintained by dosing application solution (= concentrated test item solutions) into the test water by using automatic dispenser

	units (HAMILTON, Reno, Nevada, USA). The test media were divided into four identical volumes by electronically regulated splitting devices (PEQUITEC, CH-4414 Füllinsdorf, Switzerland) and were directed to the four replicates of each treatment. The flow rate of the test media through each of the four replicate glass beakers corresponded to at least a fivefold theoretical volume exchange per day. The application solution used for the dosage of the highest test concentration was prepared by dissolving the test item completely in purified water. In a series of dilution steps, this test medium was diluted with test water to prepare the application solution used for the dosage of the lower test concentrations.
Analytics:	From the application solutions, all test media and the control duplicate samples were taken regularly during the test period. The concentrations of lacosamide were analyzed by HPLC in the test media samples from the highest test concentration of nominal 10 mg/L, determined in the experiment as the NOEC.
Observations:	The embryonic development and hatching of larvae in the control and the test concentrations was recorded each day. Larvae and juvenile fish were observed for mortality and visible abnormalities. At the end of the test the fish length, the body wet weight and the dry weight of the fish was determined.
Endpoints/Statistics:	Percent hatching success (hatching rate) was calculated for each replicate by dividing the number of hatched larvae by the number of eggs inserted. The mean development rate was calculated for each treatment. The survival rate of the test fish was calculated for each test concentration and the control by dividing the number of surviving fish by the number of larvae hatched. The LOEC and the NOEC for all parameters assessed were determined directly from the raw data. A statistical evaluation was not necessary since the results obtained from the different test concentrations were nearly equal or even slightly higher compared to the control.

Findings

The analytically measured lacosamide concentration in the test medium of 10 mg/L was in the rage of 95 to 110% of the nominal value during the exposure period. The test concentration was shown to be constant during the entire test period and therefore all biological results are related to the nominal concentrations of 10 mg/L.

The biological results at test end are given for each test parameter assessed:

Test parameter	NOEC*) (mg/L)	LOEC*) (mg/L)
Egg development and hatching rate	≥ 10	> 10
Time to hatch / development rate	≥ 10	> 10
Survival of larvae and juvenile fish	≥ 10	> 10
Fish length and weight (wet weight and dry weight) at test end	≥ 10	> 10

*) based on nominal test item concentrations

Conclusion

Summarizing the NOECs for each of the test parameters assessed, the **overall NOEC of lacosamide for early life stages of zebra fish was determined to be at least the highest test concentration of 10 mg/L.** The NOEC might be even higher, but concentrations above nominal 10 mg/L were not tested according to the guideline. The overall LOEC was determined to be >10 mg/L. **The NOEC/MEEC ratio for lacosamide in this chronic toxicity test by far exceeds a factor of 10** (>1'000; Appendix 11.2.4.3).

6.2.3.2 Effects on Reproduction of *Daphnia magna*

The effect of the test item lacosamide on the survival and reproduction of the aquatic invertebrate *Daphnia magna* was investigated in a semi-static test over 21 days following the OECD Guidelines for Testing of Chemicals, No. 211, (1998): "*Daphnia magna* Reproduction Test" (CTD Table 2.6.7.17, A45202)

Test Design

Test species:	Young female daphnids (less than 24 hours old) of a clone of the species *Daphnia magna* Straus. A clone (originally supplied by the University of Sheffield/UK) is bred in RCC's laboratories in culture medium identical to the medium used for the test.
Test design:	21 days semi-static test with test medium renewal periods of two and three days. 10 daphnids per test concentration and control were used, each test animal individually kept in 80 mL of test medium.
Test concentration:	Nominal 1.0, 3.2, 10, 32 and 100 mg lacosamide/L, in parallel with a control. Test concentrations were based on the results of a range finder test.
Test conditions:	The test was conducted in reconstituted water ("M7") with water hardness of 2.5 mmol/L (= 250 mg/L as $CaCO_3$). pH values in the test media ranged from 7.6 to 8.0, dissolved oxygen concentrations were at least 8.1 mg/L. Water temperature ranged from 19 to 20 °C. Photoperiod was 16 hours light and 8 hours darkness. Test animals were fed on each working day with a defined amount of a mixture of green algae and of fish food suspension.
Dosage:	Prior to each test medium preparation, the test medium of the highest test concentration was freshly prepared by completely dissolving the test item at a concentration of 100 mg/L (intensive stirring for 10 minutes). In a series of dilution steps, this test medium was diluted with test water to prepare the test media of the lower test concentrations.
Analytics:	From the freshly prepared test media samples were taken from three preparation dates. Additionally two stability control samples (two and three days old, with and without food) were taken at the end of two treatment periods. The concentrations of lacosamide were analyzed by HPLC in the test media samples from the nominal concentrations of 32 and 100 mg/L, determined in the experiment as the NOEC and the LOEC.
Observations:	The daphnids were observed for mortality at least three times per week. Date of first offspring and number of offspring were recorded.

Endpoints/Statistics: The reproduction rate was calculated as the total number of living offspring produced per parent female surviving until the end of the test. The NOEC and the LOEC of the reproduction rate were statistically evaluated by testing the mean reproduction rate at the test concentrations for statistically significant differences to the control value by the multiple Williams-test.

Findings

The measured test item concentrations in the analyzed test media of nominal 32 and 100 mg/L varied in the range of 84 to 104% of the nominal values at the start and the end of the renewal periods. Under the conditions of the test with food and Daphnia, lacosamide was stable during the test medium renewal periods of two and three days. All reported biological results are related to the nominal concentrations of the test item.

Taking into account the survival rates and the reproduction rates of the test animals, the highest concentration of lacosamide tested without toxic effects after the exposure period of 21 days (21-day NOEC) was 32 mg/L.

The lowest concentration tested with toxic effects (21-day LOEC) was determined to be 100 mg/L due to the statistically significantly reduced mean reproduction rate of *Daphnia magna* at this test concentration.

With exception of the reported mortality and the reduced reproduction rates, no visible abnormalities were observed at the test animals during the test.

Summary of effects of lacosamide on *Daphnia magna* over 21 days of exposure:

	Control	Lacosamide (nominal concentration in mg/L)				
		1.0	3.2	10	32	100
Mortality after 21 days of exposure (%)	0	0	0	20	0	0
Mean reproduction rate in % of control	100	90.6	96.6	88.0	94.0	80.7 *

* statistically significantly lower than the control value, results of a Williams-test, one-sided, $\alpha = 0.05$

Conclusion

The **NOEC of lacosamide to *Daphnia magna* survival and reproduction was 32 mg/L**, the LOEC was 100 mg/L. **The NOEC/MEEC ratio for lacosamide in this chronic toxicity test by far exceeds a factor of 10** (>10'000; Appendix 11.2.4.3).

6.2.4 Summary on Assessment Factors in Environmental Effect Studies

The following table summarizes the test endpoints (EC_{50} or NOEC) derived from the environmental effect studies and compares the respective risk characterization ratios (i.e., ratio of (EC_{50} or NOEC and EIC or MEEC) with the assessment factors as required by *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998)*. The detailed calculations are given in Appendix 11.2.

Test	Test Endpoint	Risk Characterization Ratio	Assessment Factor per Guideline
Microbial respiration inhibition (OECD 209)	NOEC ≥1000 mg/L	NOEC/EIC >100'000	-
Tier 1 testing			
Algal growth inhibition (OECD 201)	EC_{50} >100 mg/L	EC_{50}/MEEC >10'000	1000
Higher tier testing (chronic toxicity studies to satisfy European Union requirements; not required per *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998)*)			
Fish early life stage (OECD 210)	NOEC ≥10 mg/L	NOEC/MEEC >1'000	10
Daphnia reprotox (OECD 211)	NOEC 32 mg/L	NOEC/MEEC >10'000	10

For estimation of the EEC (expected environmental concentration) in a first tier no depletion mechanisms, metabolism in humans or dilution was assumed to reduce the concentration in surface water. In this conservative approach, the maximum expected environmental concentration (MEEC) is thus considered to be equivalent to the EEC or EIC. In fact, when accounting for dilution of the sewage water when entering surface water the risk characterization ratios would be even higher.

6.3 Summary on Environmental Fate and Effect of Released Substances

After intake of lacosamide by patients for treatment of partial-onset seizures or diabetic neuropathic pain the substance is mainly excreted in the human urine. Besides unchanged lacosamide (approximately 40% of applied dose) the major metabolite (O-desmethyl lacosamide) and a polar fraction were found in human urine exceeding 10% of applied dose. The O-desmethyl metabolite (SPM 12809) has no known pharmacological activity. These substances may reach the aquatic environment (surface water) by transport via sewage and sewage works (POTWs) (Section 6.1.1).

In the aquatic environment once entered lacosamide is mainly present in the aqueous phase. Concluding from its physicochemical propertied (Section 6.1.2.7) such as high water solubility and low octanol/water coefficient (log Kow 0.25) no relevant partitioning into sewage sludge or sediment is expected. Although not required, this is confirmed by adsorption / desorption experiments showing low adsorption to the soils and the river sediment tested (mean Koc of 9 mL/g). A similar behavior is assumed for the major urine metabolites for which chemical structures and HPLC retention times indicate to be more polar thus to have a comparable or higher water solubility than the parent molecule. In conclusion, only the parent compound, i.e. the active moiety lacosamide, was studied in this EA as the substance relevant for the environmental risk assessment.

Exposure of the terrestrial and atmospheric compartment to lacosamide or its metabolites is expected to be insignificant (Section 6.1.5.2 and Section 6.1.5.3).

Forced degradation studies with lacosamide indicate that abiotic processes like hydrolysis or photolysis do not contribute significantly to the dissipation of lacosamide from the aquatic environmental compartment (Section 6.1.3.1). In a ready biodegradability test lacosamide was not readily degraded to carbon dioxide under the given stringent test conditions (Section 6.1.3.2). However, it is assumed that the compound is degraded to some extent under more realistic test conditions in the aquatic environment. For the present EA, in a conservative approach, it was assumed that the compound and its major urine metabolites are stable in surface water once they have entered the aquatic environment.

Testing on microbial inhibition was done in an activated sludge respiration inhibition test. Due to the absence of effects up to the highest concentration tested (1000 mg/L) no adverse effects on microbial degradation processes are expected in wastewater treatment facilities. The 3-hour NOEC (EC_{15}) exceeds by far (>100'000x) the EIC (environmental introduction concentration) estimated at the point of entry of lacosamide into POTWs via sewage (Appendix 11.2.4.1).

Based on the low potential for bioconcentration (log Kow < 3.5; Section 6.1.2.7) and the overall assessment of lacosamide's environmental fate indicating exposure mainly of the aqueous phase of the aquatic compartment (Section 6.1.5), tier 1 acute toxicity testing in one aquatic species is appropriate per *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998).* One suitable test proposed is an algal species bioassay.

Lacosamide had no inhibitory effect on the growth of the green algal species *Scenedesmus subspicatus* during the exposure period of 72 hours at the test concentration of nominal

100 mg/L (highest concentration tested without toxic effects after the exposure period of 72 hours) and there were no sublethal effects observed at any dose tested. The 72-hour EC_{50} was determined to be >100 mg/L. Comparison with the MEEC for the aquatic environment resulted in an EC_{50}/MEEC ratio clearly exceeding a factor of 1000 for tier 1 testing (>10'000; Appendix 11.2.4.2). The high margin of safety indicates that no adverse effects on the aquatic community are to be expected after entry of lacosamide into surface waters via sewage and POTWs and that no higher tier testing (tier 2 or 3 testing) is required per *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July, 1998).*

Nethertheless two chronic toxicity studies, an early life stage toxicity test in zebra fish and a reproduction test in daphnids, were performed to satisfy European Union requirements. The results of these tests are very reassuring in that no adverse effects of lacosamide on the aquatic community are to be expected: the NOEC/MEEC ratio for lacosamide in the early life stage test in zebra fish by far exceeds a factor of 10 for chronic toxicity testing (>1'000; Appendix 11.2.4.3). Similarly, the NOEC/MEEC ratio for lacosamide on survival and reproduction of *Daphnia magna* by far exceeds a factor of 10 for chronic toxicity testing (>10'000; Appendix 11.2.4.3).

Although ecotoxicological data for the major urine metabolites are not available their potential risk to aquatic organisms are covered by the high margin of safety determined for lacosamide. Even if the metabolites will exhibit a 10-times higher ecotoxicity than lacosamide, which is not expected due to absence of any known pharmacological activity, an assessment factor of >1000 could be applied on this theoretical endpoint without exceeding the calculated MEEC based on active moiety. Considering that the metabolites only account for approximately 20% and 30% of the dose in human excretions the margin of safety would be even higher.

7 MITIGATION MEASURES

No potential adverse environmental effects have been identified to be associated with the proposed action. Therefore, no mitigation measures are needed.

8 ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental effects have been identified to be associated with the proposed action. Therefore, no alternative course of action is needed.

9 LIST OF PREPARERS

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- PhD in Medical Zoology.
- Master in Biology, optional subject chemistry (University of Basle).
- Project Leader and Head of Product Safety at RCC Ltd., managing a team of product safety experts.
- More than 10 years' experience in assessing the environmental safety of crop protection and biocidal products with the agro-chemical industry, including 6 years in management position (Global Head of Environmental Safety Assessments and Contracting with Syngenta Crop Protection AG).
- Experience in scientific monitoring of ecochemistry studies, preparation of environmental assessments for pesticides, biocides, veterinary and human drugs.
- Former member of the OECD Expert Group on Aquatic Risk Indicators, and of the ECPA Environmental Expert Group.

Dr. Niels Krebsfänger, Senior Toxicologist, SCHWARZ BIOSCIENCES GmbH (Project Toxicologist)

- Dr. rer. nat. and diploma in biochemistry.
- Diplomate of the American Board of Toxicology (D.A.B.T.), certified toxicologist by the Federation of European Toxicologist & European Societies of Toxicology (EUROTOX Registered Toxicologist) and Gesellschaft für Toxikologie in der Deutschen Gesellschaft für experimentelle und klinische Pharmakologie und Toxikologie (Fachtoxikologe DGPT).
- More than 9 years training and experience in general toxicology in academia, contract research and pharmaceutical industry.
- Member of several (inter)national toxicological societies and working groups (DGPT, BTS, EUROTOX, A.B.T, ISSX).

10 REFERENCES

Research Reports Cited in the Present EA Expert Report on Lacosamide

Report No.	Location in CTD	Title
A22173	4.2.3.7.7	SPM 927: Ready biodegradability in a CO_2 evolution (modified Sturm) test. Itingen, Switzerland: RCC Ltd.; January 2006
A22184	4.2.3.7.7	SPM 927: Toxicity to *Scenedesmus subspicatus* in a 72-hour algal growth inhibition test. Itingen, Switzerland: RCC Ltd.; December 2005
A22206	4.2.3.7.7	SPM 927: Adsorption/desorption of [^{14}C]-SPM 927 on soils. Itingen, Switzerland: RCC Ltd.; March 2006
A27033	4.2.3.7.7	SPM 927: Toxicity to activated sludge in a respiration inhibition test. Itingen, Switzerland: RCC Ltd.; December 2005
A45180	4.2.3.7.7	SPM 927: Toxic effects to Zebra fish (Brachydanio rerio) in an early-life stage toxicity test (OECD 210). Itingen, Switzerland: RCC Ltd.; August 2006
A45202	4.2.3.7.7	SPM 927: Effect on survival and reproduction of Daphnia magna in a semi-static test over three weeks (OECD 211). Itingen, Switzerland: RCC Ltd.; August 2006

Further References

The EA was prepared following the *'Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application' (FDA, CMC 6, Rev 1, July 1998)*

11 APPENDICES

11.1 Non-confidential Information

11.1.1 Data Summary Table

Data Summary Table on Endpoints for Lacosamide

Test	Endpoint	CTD Module / Report No. (Location in CTD)
Physical/Chemical Characterization		
Water solubility (25°C) in phosphate buffer, pH 4.5 in phosphate buffer, pH 7.5 in pure water	 Modification 1 : 28.4 mg/mL Modification 2 : 28.9 mg/mL Modification 1 : 20.1 mg/mL Modification 2 : 20.8 mg/mL Modification 1 : 30.2 mg/mL Modification 2 : 30.8 mg/mL	3.2.S.1.3 and 3.2.S.3.1
Log Kow (n-octanol / water partition coefficient) (OECD 107, shake flask method)	0.25 (mean, n=6)	3.2.S.1.3 and 3.2.S.3.1
Koc (adsorption / desorption coefficient normalized for organic carbon content of test soils) (OECD 106)	9 mL/g (adsorption) 12 mL/g (desorption)	A22206 (4.2.3.7.7)
Dissociation constant	No dissociation at environmentally relevant pH (pKa outside pH range of 1.5 to 12)	3.2.S.1.3 and 3.2.S.3.1
Vapour pressure at 25° C	$9.3 * 10^{-5}$ Pa (calculated)	3.2.S.1.3
Henry's Law Constant at 25°C	$1.14 * 10^{-11}$ atm*m^3/mol (calculated)	3.2.S.1.3

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Data Summary Table on Endpoints for Lacosamide (Continued)

Test	Endpoint	CTD Section / Report No.
Environmental Depletion Mechanisms		
Hydrolysis	Hydrolytically stable at environmentally relevant conditions, hydrolysis $T_{½} > 24$ hours	3.2.S.7.3
Photolysis	No significant degradation in solid state or aqueous solution after irradiation with 20'000 kJ/m^2 (1.2 million lux hours) or 100.000 kJ/m^2 (6 million lux hours) in aqueous solution.	3.2.S.7.3
Aerobic biodegradation (OECD 301 B, modified Sturm test)	Not readily biodegradable to carbon dioxide within 28 days under the stringent test conditions	A22173 (4.2.3.7.7)
Environmental Effects		
Inhibition of microbial respiration rate of activated sludge (OECD 209)	3-hour $EC_{50} > 1000$ mg/L 3-hour NOEC (EC_{15}) ≥ 1000 mg/L	A27033 (4.2.3.7.7)
Effects on algal growth of green alga *Scenedesmus subspicatus* (OECD 201)	72-hour ErC50/EbC50 > 100 mg/L	A22184 (4.2.3.7.7)
Fish Early Life Stage (OECD 210)	NOEC for all parameters tested ≥ 10 mg/L	A45180 (4.2.3.7.7)
Daphnia Reproduction (OECD 211)	21-day NOEC was 32 mg/L on survival and reproduction rates of *Daphnia magna*	A45202 (4.2.3.7.7)

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/s/

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