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
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

b(4)

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. has 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.

b(4)

[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.

APPEARS THIS WAY
ON ORIGINAL

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

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