

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203993Orig1s000**

**MICROBIOLOGY REVIEW(S)**

# Product Quality Microbiology Review

March 15, 2012

**NDA:** 203933

**Drug Product Name**

**Proprietary:** Onfi Oral Suspension

**Non-proprietary:** clobazam oral suspension

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

| <b>Submit</b> | <b>Received</b> | <b>Review Request</b> | <b>Assigned to Reviewer</b> |
|---------------|-----------------|-----------------------|-----------------------------|
| 2/28/2012     | 2/28/2012       | 2/29/2012             | 2/29/2012                   |

**Submission History (for amendments only):** N/A

**Applicant/Sponsor**

**Name:** Lundbeck LLC

**Address:** 4 Parkway North, Suite 200, Deerfield, IL 60015

**Representative:** Jenny Swalec

**Telephone:** 847 282 1066

**Name of Reviewer:** Steven P. Donald, M.S.

**Conclusion:** Recommended for approval

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA
  2. **SUBMISSION PROVIDES FOR:** the manufacture of an oral suspension product
  3. **MANUFACTURING SITE:** Rosemont Pharmaceuticals Ltd. (b) (4)  
(b) (4), West  
Yorkshire, (b) (4)
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Suspension, Oral, 2.5 mg/ml using oral dosing syringe packaged in (b) (4) Type III round, amber, glass bottles with a tamper-evident, child-resistant screw cap closure and will contain 120 mL of the suspension.
  5. **METHOD(S) OF STERILIZATION:** N/A
  6. **PHARMACOLOGICAL CATEGORY:** Antiepileptic drug of the benzodiazepine class for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients two years of age or older.
- B. **SUPPORTING/RELATED DOCUMENTS:** None
- C. **REMARKS:** The filing review was performed on 3/2/2012 where information was requested for 1.) test methods for the detection of *Burkholderia cepacia* complex, and 2.) validation studies for antimicrobial effectiveness testing. Su-Lin Sun, the project manager, issued an information request on 3/06/2012. The requested information is present in the subject submission and is deemed acceptable.

**filename:** N203993r1.doc

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## **Executive Summary**

### **I. Recommendations**

- A. Recommendation on Approvability -**  
NDA 203993 is recommended for approval from the standpoint of product quality microbiology.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

### **II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** The liquid drug product is compounded and filled into plastic containers.
- B. Brief Description of Microbiology Deficiencies –** No product quality microbiology deficiencies are identified based upon the information provided.
- C. Assessment of Risk Due to Microbiology Deficiencies – N/A**

### **III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
Steven P. Donald
- B. Endorsement Block**  
Stephen E. Langille - Team Leader
- C. CC Block**  
N/A

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/s/  
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STEVEN P DONALD  
03/20/2012

STEPHEN E LANGILLE  
03/20/2012

## PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number:** 203993

**Applicant:** Lundbeck LLC

**Letter Date:** 2/28/2012

**Drug Name:** Onfi (clobazam)

**NDA Type:** 505(b)(1)

**Stamp Date:** 2/28/2012

Oral Suspension

The following are necessary to initiate a review of the NDA application:

|   | Content Parameter   | Yes | No | Comments  |
|---|---|-----|----|---|
| 1 | Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately? | X   |    |   |
| 2 | Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?                               | X   |    | 3.2.P.3.3; 3.2.P.3.4, pg 13/24: USP <1111>          |
| 3 | Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?                         | X   |    | Microbial limits test: 3.2.P.5.3. PET not validated |
| 4 | Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?   |     | X  |   |
| 5 | Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?   | X   |    | 3.2.P.2; data not shown for PET                     |
| 6 | Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?  | X   |    | 3.2.P.5.1   |
| 7 | Has the applicant submitted the results of analytical method verification studies?  | X   |    | 3.2.P.5.4   |
| 8 | Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?  | N/A |    |   |
| 9 | Is this NDA fileable? If not, then describe why.  | X   |    |   |

**Additional Comments:**

The applicant provides acceptance criteria and methods validation for several microbiological tests, however validation of the antimicrobial effectiveness test procedure, as well as detection of *Burkholderia cepacia* complex, is not described.

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**Comments to be forwarded to the Sponsor:**

1. Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganisms of the *Burkholderia cepacia* complex (Bcc). We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for these species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of Bcc and cells that are acclimated to the product and the environments (e.g., warm or cold water) that may be tested.

2. We acknowledge that antimicrobial effectiveness testing of the drug product is performed according to USP<51> and that acceptance criteria for testing have been established. Please provide validation results for antimicrobial effectiveness testing with the preservative at or below the product's release and stability specification.

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Reviewing Microbiologist: Steven P. Donald

Date 3/2/2012

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Microbiology Secondary Reviewer: Stephen E. Langille, Ph.D.

Date 3/2/2012

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/s/  
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STEVEN P DONALD  
03/02/2012

STEPHEN E LANGILLE  
03/02/2012