

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203993Orig1s000**

**OTHER REVIEW(S)**



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** December 14, 2012

**To:** Russell Katz, M.D., Director  
Division of Neurology Products

**Through:** Michael Klein, Ph.D., Director  
Controlled Substance Staff

**From:** Alicja Lerner, M.D., Ph.D., Medical Officer  
Controlled Substance Staff

**Subject:** **NDA 203-993**  
**Product Name: Onfi** (Clobazam)  
**Indication:** Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients > 2 years of age  
**Dosages:** Oral Suspension: 2.5 mg/mL in 120 mL bottles  
**Sponsor:** Lundbeck LLC

**Materials reviewed:** Previous NDA 202-067, ONFI (Clobazam) tablets  
Previous IND 70,125  
CSS review for Clobazam tablets NDA 202-067 (Sep 16 2011)

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**I. BACKGROUND**

This memorandum responds to the DNP consult to provide CSS input on label changes proposed by the Sponsor in the section 9 DRUG ABUSE AND DEPENDENCE of NDA 203-99 (b) (4) ONFI oral suspension, which was submitted by Lundbeck LLC on Fed 28 2012.

Clobazam is a benzodiazepine substance that was first approved in 1970 in Australia. Clobazam was marketed under the trade names Frisium and Urbanol, as an anxiolytic since 1975, and as an

anticonvulsant since 1984. It was approved as an adjunctive treatment of epilepsy in over 80 countries and the total human exposure is estimated to be over 3.3 million patient years. On Oct 21, 2011, ONFI (Clobazam, NDA 202 (b)(4)67) was approved for treatment of Lennox-Gastaut syndrome, which is characterized by multiple seizure types, predominately of the tonic, atonic, and atypical absence variety and drop seizures. During the IND phase, the Sponsor requested and received in December 2007, orphan drug designation for clobazam for the adjunctive treatment of Lennox-Gastaut syndrome in patients 2 years of age and older.

Currently, clobazam is listed in Schedule IV of the Controlled Substances Act (CSA).

CSS was involved only at the stage of finalizing the label for section 9 DRUG ABUSE AND DEPENDENCE. All changes were related to section 9.2

#### SUMMARY OF LABEL CHANGES

The original approved label language was in accordance with the following Draft Guidance, however, the Sponsor made some changes, and then CSS became involved and provided input. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

Below is the first version of section 9.2 with CSS recommended changes in blue:

#### 9.2 Abuse

**ONFI can be abused in a similar manner as other benzodiazepines, such as diazepam.**

**The pharmacological profile of ONFI is similar to that of other benzodiazepines listed in Schedule IV of the Controlled Substance Act, particularly in its potentiation of GABAergic transmission through its action on GABAA receptors, which leads to sedation, somnolence, (b)(4)**

**The World Health Organization epidemiology database contains reports of drug abuse, misuse, and overdoses associated with clobazam.**

**Drug abuse is the intentional non-therapeutic use of a drug, even once, for its rewarding psychological or physiological effects.**

Subsequently, the Sponsor made the following changes:



2. Added to the sentence defining abuse “*repeatedly or even sporadically*”. CSS accepted this change as it is consistent with the language in Guidance for Industry.

## II. CONCLUSIONS

CSS concurred with the final version of the label proposed by the Sponsor. However, we question the Sponsor statement 2 (cited above) regarding (b) (4)

It is known that Onfi (Clobazam) was first approved in 1975, as an anxiolytic and there is a significant body of evidence that Onfi (Clobazam) is a strong anxiolytic. Multiple clinical studies have demonstrated the efficacy of clobazam as an anxiolytic medication in a variety of psychiatric disorders, such as general anxiety disorder, cardiovascular and gastrointestinal psychosomatic disorders, pediatric behavioral disorders with anxiety and restlessness, anxiety states in psychotic disorders and alcohol withdrawal (Doonagji et al, 1979; Donlon and Singer, 1979; Jacobson et al 1983; Koeppen, 1979; Lapierre et al, 1982; Laudano et al, 1977; Lemoine et al, 1996; Schjonsby et al, 1979). In these studies, clobazam was compared to placebo and a benzodiazepine, usually diazepam or lorazepam. Therapeutic trials indicate that the anti-anxiety effect of clobazam 20 to 80 mg daily is comparable with the 10 to 40 mg dose of diazepam (Broden et al 1980).

## III. RECOMMENDATIONS

We recommend that OSE be consulted to examine all reports on abuse related adverse events of the approved Onfi (Clobazam) tablets that have been on the U.S. market since October 2011.

## REFERENCES

Broden RN, Heel RC, Speight TM, Avery GS. Clobazam: a review of its pharmacological properties and therapeutic use in anxiety. *Drugs*. 1980 Sep;20(3):161-78.

Donlon PT, Singer JM. Clobazam versus placebo for anxiety and tension in psychoneurotic outpatients. A multicenter collaborative study. *J Clin Pharmacol*. 1979 May-Jun;19(5-6):297-302.

Doonagji DR, Sheth A, Apte JS, Lakdawala PD, Khare CB, Thatte SS. Clobazam versus diazepam: a double-blind study in anxiety neurosis [proceedings]. *Br J Clin Pharmacol*. 1979;7 Suppl 1:119S.

Jacobson AF, Goldstein BJ, Dominguez RA, Steinbook RM. A placebo-controlled, double-blind comparison of clobazam and diazepam in the treatment of anxiety. *J Clin Psychiatry*. 1983 Aug;44(8):296-300.

Lapierre YD, Tremblay A, Gagnon A, Monpremier P, Berliss H, Oyewumi LK A  
therapeutic and discontinuation study of clobazam and diazepam in anxiety neurosis. *J Clin Psychiatry*. 1982 Sep;43(9):372-4.

Laudano O, Peralta M, Lujan L, Aparicio N, Moizeszowicz J. Effect of a new  
benzodiazepine derivate, clobazam, in anxious patients with gastrointestinal disorders. *J Clin Pharmacol*. 1977 Jul;17(7):441-6.

Lemoine P, Rouillon F, Pouget D. Efficacy and withdrawal of clobazam, lorazepam and  
buspirone in the treatment of anxiety disorders. *Encephale*. 1996 Nov-Dec;22(6):461-7.  
Schjønby HP, Gordon AE, Koeppen D. A three-month double-blind study of clobazam  
versus diazepam in out-patients suffering from neurotic disturbances. *J Int Med Res*.  
1979;7(5):404-10.

Schjønby HP, Gordon AE, Koeppen D. A three-month double-blind study of clobazam  
versus diazepam in out-patients suffering from neurotic disturbances. *J Int Med Res*.  
1979;7(5):404-10.

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/s/  
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ALICJA LERNER  
12/14/2012

MICHAEL KLEIN  
12/14/2012

## SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

<b>Product Title</b>	<b>ONFI (clobazam) tablets, for oral use, CIV; ONFI (clobazam) oral suspension, CIV</b>
Applicant	Lundbeck
Application/Supplement Number	NDA 203993
Type of Application	Efficacy Supplement
Indication(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years of age or older
Established Pharmacologic Class <sup>1</sup>	Benzodiazepine
Office/Division	ODE I/DNP
Division Project Manager	Su-lin Sun
Date FDA Received Application	February 28, 2012
Goal Date	December 28, 2012
Date PI Received by SEALD	December 12, 2012
SEALD Review Date	December 13, 2012
SEALD Labeling Reviewer	Elizabeth Donohoe
SEALD Division Director	Laurie Burke

PI = prescribing information

<sup>1</sup> The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

# Selected Requirements of Prescribing Information

## Highlights (HL)

### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:** *The heading at the top of all pages in the document should be removed. The numbered lines should also be removed throughout the PI.*

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:** *Removal of the header will allow HL to meet the 1/2 page requirement.*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 4. White space must be present before each major heading in HL.

**Comment:**

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:**

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI

## Selected Requirements of Prescribing Information

• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

**Comment:**

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

**Comment:**

#### Product Title

- YES** 10. Product title in HL must be **bolded**.

**Comment:**

#### Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning

- N/A** 12. All text must be **bolded**.

**Comment:**

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

## Selected Requirements of Prescribing Information

### Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

### Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

### Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

### Comment:

### Recent Major Changes (RMC)

- YES** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

### Comment:

- YES** 18. Must be listed in the same order in HL as they appear in FPI.

### Comment:

- YES** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

### Comment:

- YES** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

### Comment:

### Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

### Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

### Comment:

**N/A**

## Selected Requirements of Prescribing Information

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: Because this product has a Medication Guide, the correct statement should be: “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide”. The Labeling Review Tool states that when there are two pieces of FDA-approved patient labeling, the MG takes precedence.

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: The title for 7.3 in the TOC reads: “ONFI, CNS Depressants and Alcohol” while 7.3 in the FPI reads: “CNS Depressants and Alcohol”.

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

## Selected Requirements of Prescribing Information

**Comment:**

**YES** 32. All section headings must be **bolded** and in UPPER CASE.

**Comment:**

**YES** 33. All subsection headings must be indented, not bolded, and in title case.

**Comment:**

**YES** 34. When a section or subsection is omitted, the numbering does not change.

**Comment:**

**YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

**Comment:** *This statement generally appears at the end of the 2nd column of the TOC.*

### Full Prescribing Information (FPI)

#### GENERAL FORMAT

**YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

**Comment:**

**YES** 37. All section and subsection headings and numbers must be **bolded**.

**Comment:**

**YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>

## Selected Requirements of Prescribing Information

<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

**Comment:** *The format for cross-referencing is correct in the FPI, however, many citations are incorrect. For example, in 5.3, the cross-reference should be 2.2 instead of 2.6. Many citations were not updated to reflect the new ordering of subsections in D&A; also see 8.5, 8.6, 8.7, 8.8, 9.3, 12.3 (under Age and Hepatic Impairment), 12.5 and 17 (under Increasing or Decreasing the Onfi Dose). Recommend review of entire PI for correct cross-references.*

- YES** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- N/A** 42. All text is **bolded**.

**Comment:**

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

#### Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

## Selected Requirements of Prescribing Information

### Comment:

#### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

### Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

Comment: *The current statement in this section has been substantially modified; if DNP agrees with this wording it is acceptable.*

#### Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

### Comment:

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/s/  
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ELIZABETH A DONOHOE  
12/13/2012

ANN M TRENTACOSTI  
12/13/2012  
Signing for Laurie Burke

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA #203993 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Onfi Established/Proper Name: clobazam Dosage Form: oral suspension Strengths: 2.5mg / mL		
Applicant: Lundbeck LLC Agent for Applicant (if applicable): Thomas Stothoff		
Date of Application: February 28, 2012 Date of Receipt: February 28, 2012 Date clock started after UN: N/A		
PDUFA Goal Date: December 28, 2012	Action Goal Date (if different):	
Filing Date: 04/28/2012	Date of Filing Meeting: 04/13/2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): For adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i><b>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</b></i>		
Review Classification:  <i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>  <i><b>If a tropical disease priority review voucher was submitted, review classification is Priority.</b></i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		
Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>  <i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): None				
List referenced IND Number(s): 07125				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>		✓		4/12/12 request applicant name changed to Lundbeck LLC
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input checked="" type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>	<p>✓</p>			<p>Onfi (clobazam) tablet</p>																

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>		✓		Felbamate Lamotrigine rufinamide Topiramate
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested:</b></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		✓		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		✓		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>		✓		

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	✓			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	✓			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	✓			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<ul style="list-style-type: none"> <li>✓ legible</li> <li>✓ English (or translated into English)</li> <li>✓ pagination</li> <li>✓ navigable hyperlinks (electronic submissions only)</li> </ul> <p><b>If no, explain.</b></p>				
<p><b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>				
<b>Forms and Certifications</b>				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i></p>	✓			
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	✓			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</p>	✓			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	✓			
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	✓			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p>	✓			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	✓			

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i> 12/06/2012</p>	✓			<b>12/6/12—consult CSS for PI (section 9) content.</b>

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		✓		Orphan indication—PREA waived

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?		✓		
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			✓	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			✓	
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>				
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	✓			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>			✓	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	✓			
Is the PI submitted in PLR format? <sup>4</sup>	✓			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	✓			Micro consult
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s) <b>Date(s):</b>  <i>If yes, distribute minutes before filing meeting</i>		✓		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>		✓		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		✓		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** April 28, 2012

**BLA/NDA/Supp #:** NDA # 203993

**PROPRIETARY NAME:** Onfi

**ESTABLISHED/PROPER NAME:** clobazam

**DOSAGE FORM/STRENGTH:** oral suspension (2.5mg/mL)

**APPLICANT:** Lundbeck LLC

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** For adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older.

**BACKGROUND:**

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Su-Lin Sun	Y
	CPMS/TL:	Robbin Nighswander/ Jacqueline Ware	N
Cross-Discipline Team Leader (CDTL)	Norman Hershkowitz		Y
Clinical	Reviewer:	Phillip Sheridan	Y
	TL:	Norman Hershkowitz	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Ta-Chen Wu	Y
	TL:	Angela Men	Y
Biostatistics	Reviewer:	N/A	
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Edward Fisher	Y
	TL:	Lois Free	N
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Akm Khairuzzaman	Y
	TL:	Martha Heimann	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Steven Donald	Y
	TL:	Stephen Langile	N
ONDQA	Reviewer:	Akm Khairuzzaman	Y
	TL:	Angelica Dorantes	Y
Facility Review/Inspection	Reviewer:	NA	
	TL:		
OSE/DMEPA	Reviewer:	Kimberly De Fronzo	Y
	TL:	Todd Bridges	N
OSE (RPM)	Reviewer:	Laurie Kelley	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Xikui Chen	N
	TL:	Michael Skelly	Y
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers	Eric Brodsky (SEALD team)		Y
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b> N/A (not NME)</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<p><i>or efficacy issues</i></p> <ul style="list-style-type: none"> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b> Tablet and oral suspension use the same PI (which was recently approved on Oct 2011)</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments: Information request sent on March 6, 2012</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>RPM Labeling Review</u></b>	
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Russell G. Katz ( DNP Division Director)	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
Comments:	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> </ul>

	<ul style="list-style-type: none"> <li>notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

Su-Lin Sun, Pharm D

April 12, 2012

Regulatory Project Manager  
Robbin Nighswander

Date  
April 20, 2012

---

Chief, Project Management Staff

Date

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/  
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SU-LIN SUN  
12/11/2012

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** November 20, 2012

**To:** Su-Lin Sun, PharmD  
Senior Regulatory Project Manager  
Division of Neurology Products (DNP)

**From:** Quynh-Van Tran, PharmD, BCPP  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)  
Division of Professional Drug Promotion (DPDP)

**Subject:** OPDP Comments on draft Prescribing Information (PI), carton and container labeling for ONFI™ (clobazam) oral suspension, CIV  
  
NDA 203993

---

This consult is in response to DNP's request for DPDP's review of the labeling materials for ONFI (clozabam) oral suspension.

We appreciate the opportunity to provide comments on the PI (FDA eroom version updated 11/13/2012). Please see attached PI with our comments incorporated therein.

We have no comments on the carton and container labeling for Onfi.

If you have any questions, please contact Quynh-Van Tran, (301) 796-0185, or quynh-van.tran@fda.hhs.gov.

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/s/  
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QUYNH-VAN TRAN  
11/20/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: **November 16, 2012**

To: **Russell Katz, MD, Director  
Division of Neurology Products (DNP)**

Through: **LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
Division of Medical Policy Programs (DMPP)**

**Melissa Hulett, RN, BSN, MSBA  
Team Leader, Patient Labeling Team  
Division of Medical Policy Programs (DMPP)**

From: **Sharon W. Williams, MSN, BSN, RN  
Patient Labeling Reviewer  
Division of Medical Policy Programs (DMPP)**

Subject: **DMPP Review of Patient Labeling (Medication Guide)**

Drug Name (established name): **ONFI (clobazam)**

Dosage Form and Route: **Tablets and Oral Suspension**

Application Type/Number: **203993**

Applicant: **Lundbeck, Inc.**

## 1 INTRODUCTION

ONFI (clobazam) Tablets was originally approved under NDA 202067 on October 21, 2011 as an adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ages 2 years and older.

On February 28, 2012, Lundbeck, Inc. submitted NDA 203993 for an oral suspension formulation of ONFI (clobazam) with the same indication as the previously approved ONFI Tablets. The proposed new oral suspension formulation is targeted for LGS patients who have difficulty swallowing. The submission of NDA 203993 includes the formulations for the ONFI (clobazam) Tablets and the Oral Suspension.

This focused review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for ONFI (clobazam) Tablets and Oral Suspension.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the MG and IFU was completed on October 29, 2012.

## 2 MATERIAL REVIEWED

- Draft ONFI (clobazam) MG received on February 28, 2012 revised by the Review Division throughout the current review cycle and received by DMPP on November 13, 2012.
- Draft ONFI (clobazam) IFU received on February 28, 2012 and received by DMPP on November 13, 2012.
- Draft ONFI (clobazam) Prescribing Information received February 28, 2012 revised by the Review Division throughout the current review cycle and received by DMPP on November 13, 2012.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the prescribing information (PI)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed MG and IFU review comments are collaborative DMPP and DMEPA.

#### **4 CONCLUSIONS**

The MG and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG and IFU are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/  
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SHARON W WILLIAMS  
11/16/2012

MELISSA I HULETT  
11/16/2012

LASHAWN M GRIFFITHS  
11/16/2012

**MEMORANDUM**

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

---

DATE: October 31, 2012

TO: Russell G. Katz, M.D.  
Director, Division of Neurology Products  
Office of New Drugs

FROM: Xikui Chen, Ph.D.  
Pharmacologist, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGC)  
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations  
and  
William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 203-993, Onfi (clobazam)  
oral suspension, 2.5 mg/mL, Sponsored by Lundbeck LLC,  
USA

At the request of the Division of Neurology Products, the Division of Bioequivalence and GLP Compliance (DBGC) conducted an audit of the clinical and analytical portions of the following bioequivalence study:

**Study Number:** 14033A  
**Study Title:** "Randomized, open-label, two-way crossover study investigating the relative bioavailability of Lu-00-638 (clobazam) oral suspension relative to oral tablets following a single 20 mg dose in healthy subjects"

**Clinical Site:** Sea View Research  
Miami, FL

The clinical portion of the study was audited at Sea View Research in Miami, FL by ORA Investigator Craig Garmendia of FLA-DO. Bioequivalence reserve samples were collected from Sea View Research and forwarded to the Division of Pharmaceutical Analysis in St. Louis. Following the inspection (conducted (b) (4)), no objectionable conditions were observed and Form FDA 483 was not issued.

**Analytical Site:**

(b) (4)  
(b) (4)

The analytical portion of the study was audited at (b) (4)

(b) (4) by ORA Investigator (b) (4). The audit included a thorough examination of study records, facilities, and equipment, and interviews and discussions with the firm's management and staff. Following the inspection at (b) (4), Form FDA 483 was issued (Attachment 1). OSI received the firm's response (dated October 12, 2012) to the Form FDA 483 observations (Attachment 2). Our evaluation of the Form FDA 483 observations and the response from (b) (4) follows:

- 1. Failure to document all aspects of sample storage and handling during conduct of study 14033A. Specifically,**
  - a) There was no record of times and dates when calibrators, quality control samples, and study samples were removed from freezers and replaced after analyses, or the durations while they were thawed.**
  - b) There was no record of thawing and refreezing of study samples. Instead, there were only one or two ink marks on sample tube caps to indicate one or two thawings of calibrators and quality control samples.**

Times and dates for movement of calibrators, quality control samples, and study samples in and out of freezers were not tracked. Thawing durations and refreezing of these samples were not recorded. The firm should have documented the details for samples' movements. However, stability during three freeze/thaw (F/T) cycles was demonstrated, and no sample was processed with more than three F/T cycles, according to records of analytical runs in Watson LIMS for study 14033A. It is unlikely that the conditions of sample storage and handling exceeded those for which stability was demonstrated.

In their response, the firm will update SOP\_00372 "Procedure for use of laboratory books" and SOP\_00401 "Procedure for use of standard substances and reagent log" to record the time and date for sample movement in and out of freezers, and the actual number of freeze/thaw cycles.

The firm's response is reasonable and analytical data of the study are acceptable for agency review.

**Conclusion:**

Following the above inspections, the DBGC reviewer recommends that the clinical and bioanalytical portions of study 14033A be accepted for agency review.

**Final Classifications:**

**NAI-** Sea View Research, Miami, FL  
FEI 3005611026

**VAI-** [REDACTED] (b) (4)

cc:

OSI/Moreno

OSI/DBGK/Taylor/Haidar/Skelly/Dejernet/Chen/CF

OND/DNP/Katz/Sun

BLT-DO/Secrist

FLA-DO/Garmendia

CDER DSI PM TRACK

Draft: XC 10/3/2012

Edit: MFS 10/3/2012; SHH 10/31/2012, WHT 10/31/2012

DSI: BE 6337

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FACTS: 1405758

[REDACTED] (b) (4)

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/s/  
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XIKUI CHEN  
10/31/2012

SAM H HAIDAR  
10/31/2012

WILLIAM H TAYLOR  
11/01/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: October 29, 2012

Reviewer: Kimberly DeFronzo, RPh, MS, MBA  
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh  
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh  
Division of Medication Error Prevention and Analysis

Division Director: Carol A. Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Onfi (Clobazam) Oral Suspension  
2.5 mg/mL

Application Type/Number: NDA 203993

Applicant: Lundbeck Inc.

OSE RCM #: 2012-528

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## **1 INTRODUCTION**

This review evaluates the proposed container label, carton and insert labeling, Instructions for Use, and oral syringe dosing device for Onfi (Clobazam) Oral Suspension NDA 203993 for areas of vulnerability that could lead to medication errors.

### **1.1 BACKGROUND**

On February 28, 2012, Lundbeck submitted a NDA 203993 for an oral suspension formulation of Onfi (Clobazam) with the same indication as the previously approved Onfi Tablets, for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ages 2 years and older. The proposed new oral suspension formulation is targeted for LGS patients who have difficulty swallowing tablets.

As per the February 28, 2012, NDA 203993 submission, the Applicant proposes the oral suspension formulation to be bioequivalent to the approved tablets; therefore, no clinical efficacy studies were performed and CMC information is being cross-referenced to the approved NDA 202067 for the tablet formulation.

On July 19, 2012, the Applicant submitted additional data on the bioequivalence study that was conducted for the oral suspension and provided new stability data which extended its original (b) (4) stability data to 90-day stability. A revised insert labeling was submitted to reflect the additional data as well as other editorial changes.

On July 25, 2012, the Applicant responded to the Information Request initiated by DMEPA and provided clarifications regarding the oral syringe dosing device. Accordingly, the Applicant also submitted a revised "Instructions for Use" labeling which reflects the Applicant's responses to DMEPA's questions.

The Patient Labeling group of CDER has also been consulted to review the Instructions for Use and will provide comments in a separate review.

### **1.2 REGULATORY HISTORY**

Clobazam is marketed in most of the world by Aventis for the treatment of anxiety and epilepsy under the brand name Frisium. Clobazam is sold under the brand name Novo-Clobazam in Canada, other brand names, or under the generic name, Clobazam in ex-U.S. countries. Clobazam is available worldwide in different dosage formulations including tablet, capsule, oral solution, and oral suspension. However, Clobazam is currently only available as a tablet formulation in the U.S. under the brand name Onfi.

Orphan drug designation was granted to Clobazam on December 18, 2007, for the treatment of LGS. On October 21, 2011, Lundbeck received U.S. approval for Onfi (Clobazam) Tablets under NDA 202067. No REMS was required for this approval. This product is a Scheduled IV Controlled Substance.

### **1.3 PRODUCT INFORMATION**

The following product information is provided in the February 28, 2012, submission and July 19, 2012, submission containing revised insert labeling.

- Active Ingredient: Clobazam

- Indication of Use: for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older
- Route of Administration: Oral
- Dosage Form: Suspension
- Strength: 2.5 mg/mL
- Dose and Frequency:
  - Patients  $\leq$  30 kg body weight: 5 mg daily and titrate as tolerated up to 20 mg daily
  - Patients  $>$  30 kg body weight: 10 mg daily and titrate as tolerated up to 40 mg daily
  - Doses above 5 mg/day should be administered in two divided doses
- How Supplied: Onfi oral suspension is a berry flavored off-white liquid supplied in a bottle with a child-resistant closure. A push-in-bottle adapter along with two 10-mL oral dosing syringes is also provided.

All inactive ingredients except the berry flavor are compendial and are commonly used as excipients in oral dosage forms. The composition of the berry flavor is given in the manufacturer's DMF (b) (4).

- Storage: Store the oral suspension in an upright position. Use within 90 days of first opening the bottle, then discard any remainder. Store at 20-25°C (68-77° F). See USP controlled room temperature.
- Container and Closure System: The drug product will be packaged in a (b) (4) Type III, round, amber glass bottle with a (b) (4) tamper evident, child-resistant screw-cap closure. Each bottle contains 120 mL of the suspension and is intended for multi-dose. (b) (4)
- Stability Data: In the insert labeling under "How Supplied" section 16, DMEPA notes the Applicant provided the statement "Use (b) (4) within 90 days of first opening bottle, then discard any remainder" based upon stability data submitted by Applicant. We find the proposed size of 120 mL (2.5 mg/mL) bottle would provide enough medication for a 60-day supply at the lowest recommended dose of 5 mg (or 2 mL) per day. Therefore, we find the bottle size to be appropriate and does not pose a concern with medication being left over beyond the 90-day expiration period as supply would be depleted by 60 days under normal setting.

## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS for Onfi medication error reports. We also reviewed the Onfi labels and labeling submitted by the Applicant, searched PubMed and the ISMP publications, and reviewed previous DMEPA review for Clobazam.

## 2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) using the strategy listed below in Table 1.

<b>Table 1: AERS Search Strategy</b>	
Date	Search conducted on 6/15/12. No time limitation used.
Drug Names	Clobazam as the active ingredient Onfi as the trade name Cloba% as the verbatim term
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The AERS database search identified 55 reports. Each report was reviewed for relevancy and duplication. After individual review, 52 reports were not included in the final analysis for the following reasons:

1. Suicide attempt or intentional overdose (n=34)
2. Medication error did not involve Onfi (n=10)
3. Drug was given to wrong patient (n=4)
4. Lack of efficacy/product quality issue (n=3). These reports have been forwarded to DQRS for their attention.
5. Missed dose/medication not administered as scheduled (n=1)

## 2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on June 15, 2012, for additional cases and actions concerning Onfi. However, no medication error reports were identified in either source.

## 2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label submitted February 28, 2012 (Appendix B)

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Carton Labeling submitted February 28, 2012 (Appendix C)
- Revised Insert Labeling submitted July 19, 2012 (no image)
- Revised Instructions for Use submitted July 25, 2012 (no image)
- Oral syringe dosing device (sample provided by Applicant)
- Bottle with child-resistant cap and bottle adapter (sample provided by Applicant)

## 2.4 PREVIOUSLY COMPLETED REVIEWS

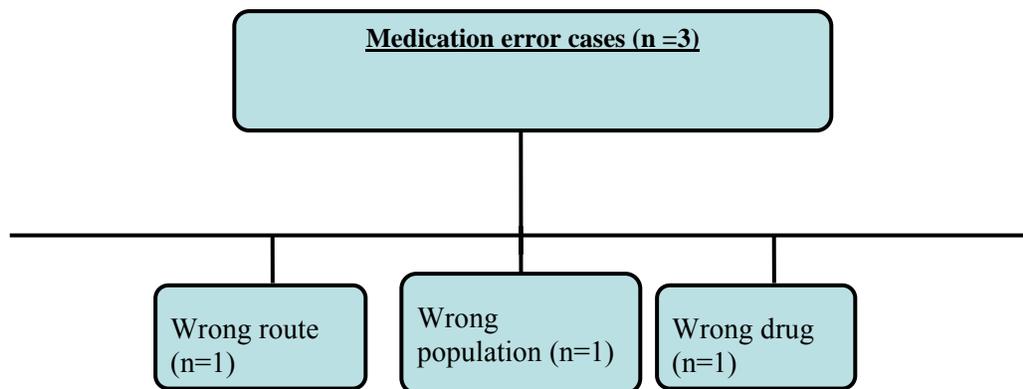
DMEPA reviewed the label and labeling of Onfi (Clobazam) Tablets under OSE RCM # 2011-189 (dated May 26, 2011), and evaluated the revised label and labeling submitted by the Applicant in response to the labeling recommendations made by DMEPA (under the same OSE RCM # 2011-189 dated August 29, 2011). No prior review was conducted for the oral suspension formulation of Onfi.

## 3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

### 3.1 MEDICATION ERROR CASES (n = 3)

Following exclusions as described in section 2.1, only three Onfi medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter<sup>2</sup>. Figure 1 provides a stratification of the number of cases included in the review by type of error. Details regarding these cases can be found in Appendix D.

**Figure 1: Onfi medication errors (n = 3) categorized by type of error**



<sup>2</sup>The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed on June 1, 2011.

**Wrong route (n = 1)**

This was a case involving a 3 year old male child who was inadvertently administered crushed clobazam through a central venous line rather than an NG tube. As the drugs were being administered the patient developed circumoral cyanosis and decreased blood pressure but returned to normal after a few minutes. No other detail was provided in the report (ISR #4138599).

**Wrong population (n = 1)**

This was a report involving a neonate male patient with congenital microcephaly (MIC). Fifteen minutes after birth, the patient experienced seizure activity and was treated with clobazam (unspecified), amongst a number of other medications for seizures. The patient's outcome for the events was not reported (ISR #7794093).

**Wrong drug (n = 1)**

This case involved a physician entering an order via CPOE for clonazepam 2.5 mg instead of “clobazam- 2.5 mg PO BID”. The reporter stated the medication error was due to the two medications having similar sounding names (clonazepam vs. clobazam) and similar dosing (ISR #8362997).

**3.2 EVALUATION OF PROPOSED ORAL FORMULATION FOR MEDICATION ERROR POTENTIAL**

We received a report of Onfi tablets being crushed and inadvertently administered intravenously instead of through an NG tube. Since this wrong route medication error occurred with the tablet formulation of Onfi, the introduction of an oral liquid formulation of Onfi will provide a formulation that is easier to swallow and may decrease the risk of crushing errors. This formulation is not provided in unit-dose sizes and supplied with an oral syringe that can not accommodate a needle or be attached to a needless system. However, if the product is used as a bulk bottle in an inpatient setting, the oral syringes may be used and then discarded. In this scenario, it is important that the labels and labeling clearly convey the oral route of administration to the healthcare provider so that the healthcare provider can select another oral syringe to prepare the dose of medication. Statements such as “For Oral Administration” will help bring attention to the route of administration on the label.

Additionally, since we have postmarketing reports of administration of tablet dosage form being given by NG tube, we need to ensure this oral suspension can be given via NG tube without clogging the tube. A discussion with ONDQA confirmed that this product is a very viscous product and has not been studied for NG tube administration. However, ONDQA has requested additional information from the Applicant regarding the resuspendibility of the product which may assist with the risk assessment of NG tube clogging. If there is an issue with the administration of this product through an NG tube, then a warning against the administration of this product via NG tube should be added on the container label and the Dosage and Administration section to inform the user on the proper route of administration for this product. The proposed insert labeling is currently silent on this issue. In order to further reinforce the oral route of administration of this

product, the statement “For Oral Administration” should also be prominently added to the oral syringe barrel.

Moreover, Onfi is only approved for patients 2 years of age or older. However, a postmarketing medication error case described the administration of this product to a neonate. DMEPA acknowledges that the current in-use and proposed labeling for Onfi provide an age for the approved patient population as 2 years of age or older under the Indication and Usage section. However, no age guideline is provided in the Dosage and Administration section where prescribers typically consult for dosing instructions. The omission of the approved age from the Dosage and Administration section may predispose administration of this product to a pediatric population below the approved age of 2 years, especially since dosing for this product is weight-based and the dosing guidelines provide for a dose at  $\leq 30$  kg body weight. We recommend adding a statement such as “The safety and effectiveness in patients less than 2 years of age have not been established”, or “This product is only approved for patients 2 years of age or older”, to the Dosage and Administration section in the Highlights of Prescribing Information and in section 2.1 (similar to the language found in section 8.4 under Use in Specific Populations or Indications and Usage sections, respectively) as a reminder to prescribers of the approved age range, especially since the oral suspension formulation may increase its use due to ease of administration to a child compared to the tablet.

Additionally, we note the size of the oral syringe is appropriate for the product since the 10 mL size syringe can accommodate the recommended maximum daily dose of Onfi Oral Suspension 40 mg/16 mL (since doses above 5 mg/day is given in two equally divided doses of 8 mL per dose). In order to better understand the rationale why the Applicant selected to include two oral syringes in each package, an information request was submitted to the Applicant. The Applicant confirmed via written correspondence the following reasons:

A syringe dose accuracy study after cleaning was performed by (b) (4) (the syringe manufacturer). In that study, only 30 cleaning cycles were performed. For a patient on a dose of up to 10 mg per day (5 mg dose, twice a day), the number of doses that can be given from the suspension bottle would be 60 doses. Assuming the patient washes the syringe after each dose, the number of syringe washes would be 60, which clearly exceeds the number of cleaning cycles performed in the study by (b) (4). Therefore, two syringes have been included with the product. Further, if the patient accidentally compromises a syringe (breakage or misplaced syringe), a second syringe would be readily available for use. The inclusion of two syringes is also consistent with recently approved products (eg. Sabril and Banzel).

The rationale provide by the Applicant appears reasonable. However, we recommend the Applicant provide this rationale in the labeling to properly inform the user of the purposes of each syringe to avoid confusion and mitigate medication errors of double dosing with the two syringes. Moreover, there is no reminder on the container label or carton labeling to use only the oral syringes provided with product. The insert labeling under Dosage and Administration section does include such a statement so the

container and carton should match that information to ensure consistency of the message.

Additionally, we provide other recommendations in section 4 which may help improve clarity and readability of important information concerning this product.

#### 4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling as well as the Instructions for Use contain confusing or misleading language, missing important steps, and provide ineffective diagrams that require a number of revisions prior to approval.

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA.

##### Comments to the Division:

###### A. Insert Labeling

1. Update the Medication Guide under “How should I store Onfi?” heading, and the Instructions for Use under step 8 with the new 90-days stability data from the previous (b) (4) stability data.
2. Revise the storage condition statement to include the units °C or °F, respectively, and replace the hyphen within the temperature designations with the word “to” for improved clarity and to be consistent with USP standards. We recommend not using the hyphen between the numbers because a hyphen can be misinterpreted as a minus sign when discussing temperatures. Therefore, revise the statement “Store at 20-25°C (68-77°F)...” to read “Store at 20°C to 25°C (68°F to 77°F)...”
3. Add a statement such as “The safety and effectiveness in patients less than 2 years of age have not been established” or “This product is only approved for patients 2 years of age or older” to the Dosage and Administration section in the Highlights of Prescribing Information and section 2.1 (similar to what is found in section 8.4 under Use in Specific Populations or Indications and Usage sections, respectively) as a reminder to prescribers of the approved patient population of 2 years of age or older.
4. Revise the reference statement (b) (4) at the end of the Dosage and Administration section 2.1 to read “Instructions for Use Onfi (clobazam) Oral Suspension” to reflect the correct title of this instructional leaflet.
5. Under the How Supplied section, revise the “Onfi oral suspension is...” sentence to read:

Onfi oral suspension is a berry flavored off-white liquid containing 2.5 mg/mL clobazam supplied in a bottle with a tamper evident, child-resistant screw-cap closure.
6. Consider reorganizing the information provided in the Medication Guide under the “How should I take Onfi” section as follows:

- a) Provide general information applicable to both tablet and suspension formulations at the top of this section. For example: Relocate your current statements such as “Take Onfi exactly as your healthcare provides...”, etc. to the beginning of this paragraph.
- b) Followed by information applicable only to the tablet formulation. For example: “Onfi tablets can be taken whole...”
- c) Followed by the information that is applicable only to the suspension formulation. For example: “Onfi oral suspension should be shaken well in the bottle...”

## B. Instructions for Use

1. Correct the title of this document by adding an ‘s’ to the word “Instruction” in the title “Instructions for Use”.
2. Provide the rationale for including two syringes with the product. Also, provide instructions to the user regarding the handling of these two syringes. Clearly state the rationale and provide instructions for use of both syringes to prevent confusion among caregivers and prevent inadvertent doubling of the dose. For example, in the Instructions for Use under the “Prepare Onfi Oral Suspension Dose” section, additional instructions can be added to the third bullet point such as “Oral dosing syringe (2 dosing syringes are included in the Onfi oral suspension box with one syringe being used for xxx...and the second syringe being used for yyy...). Similar clarifications can be achieved by adding more language under subtitle “Oral Dosing Syringes” to clarify the purpose of the second syringe using statements such as “Use only one syringe at a time for dosing and the other syringe should only be used when the markings are no longer legible...” (or similar language).
3. Remove the (b) (4) The (b) (4) currently references a (b) (4) which may mislead the patient to inadvertently take their prescribed total daily dose (b) (4) since the divided dosing schedule is recommended only for doses above 5 mg/day which is not applicable to all patients. In addition, the dose may be escalated every 7 days by the physician so this (b) (4) could actually cause confusion and dosing errors especially if more than one care giver administers the medication to the patient. Please remove this same (b) (4) reference from Step 4.
4. Add the statement “Do not exceed the prescribed total dose in one day” (or similar language) in Step 4 to reinforce this important concept.
5. At the end of the instructions in Step 5, add the words “through the opening in the bottle adapter” so that the revised statement should read “Push the plunger all the way down and then insert the syringe into the upright bottle through the opening in the bottle adapter.”

6. In Step 6, add the phrase “prescribed by your doctor” to the end of the instructions to read “the amount of liquid medicine prescribed by your doctor in Step 4”.
7. The picture in Step 7 doesn’t correspond with the directions “corner of your child’s mouth”. Replace the picture to better illustrate administering the medication into the corner of the child’s mouth.
8. Replace the “(b) (4)” stability data with the new 90-days stability data located above Figure I.
9. Due to integrity issues with washing the oral syringes in a dishwasher,<sup>1</sup> we recommend adding another statement, such as “Avoid washing the oral syringe in the dishwasher”, and add specific instructions to only manually wash the oral syringes in the last Step since the use of the word (b) (4) is ambiguous and implies that other options are equally acceptable while this is not the case.

Comments to the Applicant:

C. Container Label and Carton Labeling

1. Increase the prominence of the statement “For Oral Administration” on the principal display and side panels by bolding and/or adding more white space around this statement (or by some other means) to help highlight this important information and minimize the potential for wrong route medication errors.
2. Revise the phrase “Instructions for (b) (4)” on the principal display panel to read “Instructions for Use” to reflect the correct name of the document.
3. Remove the hyphen and revise the Storage statement to read “Store at 20°C to 25°C (68°F to 77°F)” rather than “Store at 20-25°C (68-77°F)” to be consistent with current USP designations.
4. Replace the word (b) (4) with the word “Lot” and replace the word (b) (4) to the more commonly used term in the United States of “expiration” or “Exp”. Ensure this information is consistent on both container label and carton labeling.

D. Oral Syringe

1. Include the following statements on the barrel of the oral syringes:  
“For Use with Onfi Oral Suspension Only.”  
“For Oral Administration Only.”

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<sup>1</sup> Data obtained from Quality Section 3 within NDA 203993 submitted on February 28, 2012: “The manufacturer recommends that the oral dispensers should be manually cleaned only using warm water along with dish washing soap. The use of a domestic dishwasher is not recommended for cleaning the oral dispensers.” (b) (4)

If you have further questions or need clarifications, please contact Laurie Kelley, OSE Project Manager, at 301-796-5068.

## **APPENDICES**

### **APPENDIX A. DATABASE DESCRIPTIONS**

#### **Adverse Event Reporting System (AERS)**

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

1 Page of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

**Appendix D:** Details of medication error cases identified from AERS database

Narrative
<p>This was a case involving a 3 year old male child who was placed on therapy with crushed topiramate 87.5 mg/twice a day via NG (nasogastric) tube in 2002 for the treatment of seizures. Concomitant therapy included lamotrigine (72.5 mg/day via NG) tacrolimus (4 mg/day via NG), loperamide (2 mg/day via NG) and clobazam (15mg/day via NG). On <span style="background-color: #cccccc; border: 1px solid black; padding: 0 20px;">(b) (6)</span> the patient was inadvertently administered topiramate, lamotrigine, tacrolimus, loperamide and clobazam through a central venous line rather than an NG tube. The drugs were all mixed together in a syringe. As the drugs were being administered the patient developed circumoral cyanosis and decreased blood pressure. The drug administration was stopped and the patient was administered oxygen, saline, and epinephrine for "questionable" anaphylaxis. In a few minutes the patient began breathing on his own and his blood pressure was normal. He was transferred to the intensive care unit for observation and put on antibiotics. No other detail was provided in the report (ISR #4138599). Therefore, the root cause for this wrong route medication error can not be determined at this time.</p>
<p>This was a report involving a neonate male patient (ISR #7794093). The patient had congenital microcephaly (MIC) with numerous capillary malformations. Fifteen minutes after birth the patient experienced seizure activity and was treated with topiramate (unspecified formulation, unspecified dose). Additional suspect drugs included clobazam (unspecified), amongst a number of other medications for seizures. Concomitant medications were not reported and action taken with the suspect drugs: topiramate, phenobarbital, fosphenytoin, rufinamide, vigabatrin, clobazam, felbamate, levetiracetam, clonazepam, pyridoxine, and lorazepam were not reported. The patient's outcome for the events was not reported.</p>
<p>This case involved a physician entering an order via CPOE for clonazepam 2.5 mg x 1 dose (ISR #8362997). The pharmacist performed a series of steps for verification (which included checking the dosing of clonazepam and noting it was a high dose but within range; looked at what the patient received in the hospital and saw the dose was the same; called the RN on the floor to clarify the order, and the RN confirmed the patient was to receive "plain clonazepam"). Subsequently, the patient was discharged with an order for "clonazepam- 2.5 mg PO BID". About 4 hours after discharge, the patient was presented at the emergency room (ER) with complaints of sedation and "not acting like himself". The ER physician discovered that the medication the patient should have been on was "clobazam- 2.5 mg PO BID". The reporter stated the medication error was due to the two medications having similar sounding names (clonazepam vs. clobazam) and similar dosing. DMEPA acknowledges the similarity of these two established names. However, since this is the only report of product name confusion with clobazam identified in the AERS database, DMEPA will monitor these errors through our routine post-marketing surveillance to help determine if any risk mitigation strategy is warranted for these products.</p>

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KIMBERLY A DE FRONZO  
10/29/2012

CAROL A HOLQUIST  
10/29/2012

## Division of Neurology Products

### REGULATORY PROJECT MANAGER LABELING REVIEW

**Application:** NDA 203993

**Name of Drug:** Onfi (clobazam) oral suspension

**Applicant:** Lundbeck LLC

### Labeling Reviewed

**Submission Date:** February 28, 2012

**Receipt Date:** February 28, 2012

#### Background and Summary Description:

- Onfi (clobazam) tablet was approved in October, 2012. This new drug application is for new dosage form (oral suspension 2.5 mg/mL)
- This new drug application provides for the use of clobazam for the proposed indication for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patient 2 years of age or older.
- Clobazam received Orphan Designation, so it's exempt from the PREA requirement.

### Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. Labeling deficiencies are identified in this section with a "NO" in the drop-down box next to the labeling requirement.

In addition, the following labeling issues were identified:

- The Highlights must list recent major change (RMC) in section 2.2 of the prescribing information (e.g., administration information about ONFI oral suspension).
- Use bulleted subheading for each dosage form type.

- In the Highlights, the Patient Counseling Information Statement must include following bolded verbatim statement: “See 17 for PATIENT COUNSELING INFORMATION And FDA-Approved Patient Labeling” because of the additional patient-labeling (i.e., Patients Instructions for Use).
- If a RMC is listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.
- Remove the periods after the numbers in each Section (for example, use "4" instead of "4.")
- Please change “See FDA-Approved Patient Labeling (Medication Guide)” to “See FDA-Approved Patient Labeling (Medication Guide and Instructions for Use)”.

### **Recommendations**

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 28, 2012. The resubmitted labeling will be used for further labeling discussions.

Su-Lin Sun

April 27, 2012

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Regulatory Project Manager

Date

Robbin Nighswander

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Chief, Project Management Staff

Date

# Selected Requirements of Prescribing Information (SRPI) Revised

Selected Requirement of Prescribing Information Revised (SRPI-Revised) is a drop-down checklist of critical elements of the prescribing information (PI) used during labeling review. The SRPI-Revised replaces the SRPI and includes only PI format items.

For additional information concerning the content and format of the PI, see regulatory requirements (21 CFR 201.56 and 201.57), labeling guidances, and the Labeling Review Tool at: <http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/UCM284987.doc>.

**Instructions:** There is one drop-down menu and one comment field for each item.

**Drop-Down Menu:** For each item, click on the word “**NO**” and choose one of three options (since **NO** is the default option, review each item and select the appropriate option):

- **YES:** The PI meets the requirement for this item (**not** a deficiency).
- **NO:** The PI **does not** meet the requirement for this item (deficiency).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

**Comment Field:** Comments are optional. To insert a comment, click on the word “**Comment**” for a particular item and start typing.

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## Selected Requirements of Prescribing Information (SRPI) Revised

### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.
- Comment:**
- YES** 2. HL is one-half page or less than one-half page (the HL Boxed Warning does not count against the one-half page requirement). If longer than one-half page:
- Filing Period (Regulatory Project Manager Physicians’ Labeling Rule (PLR) Format Review): RPM has notified the Cross-Discipline Team Leader (CDTL).
  - End-of Cycle Period: A waiver has been or will be granted by the review division.
- Comment:**
- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.
- Comment:**
- YES** 4. White space must be present before each major heading in HL.
- Comment:**
- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).
- Comment:**
- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present**
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* See Recent Major Changes section below.

\*\* Virtually all product labeling should include at least one Warning and Precaution.

**Comment:**

## Selected Requirements of Prescribing Information (SRPI) Revised

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).  
Comment:

### HIGHLIGHT DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.  
Comment:

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”  
Comment:

#### Product Title

- YES** 10. Product title in HL must be **bolded**.  
Comment:

#### Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.  
Comment:

#### Boxed Warning

- N/A** 12. All text must be **bolded**.  
Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).  
Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.  
Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)  
Comment:

- N/A** 16. Should use sentence case for summary (combination of uppercase and lowercase letters typical in a sentence).  
Comment:

## Selected Requirements of Prescribing Information (SRPI) Revised

### Recent Major Changes (RMC)

- N/A** 17. Other than these five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions, there are no other sections noted in RMC.

*Comment:*

- N/A** 18. Must be listed in same order in HL as they appear in FPI.

*Comment:*

- N/A** 19. Includes heading(s) and if appropriate subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010".

*Comment:*

- NO** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

*Comment:* *Must List Recent Major Change (RMC) In Section 2.2 Of The Prescribing Information (E.G., Administration Information About ONFI Oral Suspension).*

### Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

*Comment:*

### Dosage Forms and Strengths

- NO** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

*Comment:* *Bulleted Subheading For Each Dosage Form Type.*

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

*Comment:*

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

*Comment:*

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**". Only includes a U.S. phone number.

*Comment:*

## Selected Requirements of Prescribing Information (SRPI) Revised

### Patient Counseling Information Statement

- NO** 26. Must include one of the following **bolded** verbatim statements:

Product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

Product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

*Comment: In The Highlights, The Patient Counseling Information Statement Must Include Following Bolded Verbatim Statement: “See 17 For PATIENT COUNSELING INFORMATION And FDA-Approved Patient Labeling” Because Of The Additional Patient-Labeling (I.E., Patients Instructions For Use).*

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warnings) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk

## Selected Requirements of Prescribing Information (SRPI) Revised

and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

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### Full Prescribing Information (FPI)

#### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

## Selected Requirements of Prescribing Information (SRPI) Revised

### Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI at approval.

### Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.1)*].

### Comment:

- NO** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *If A RMC Is Listed In HL, The Corresponding New Or Modified Text In The FPI Sections Or Subsections Must Be Marked With A Vertical Line On The Left Edge.*

## FULL PRESCRIBING INFORMATION DETAILS

### Boxed Warning

- N/A** 42. All text is **bolded**.

### Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

### Comment:

- N/A** 44. Should use sentence case (combination of uppercase and lowercase letters typical in a sentence) for the information in the Boxed Warning.

### Comment:

### Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

### Comment:

### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

## Selected Requirements of Prescribing Information (SRPI) Revised

### Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

### Comment:

### **Patient Counseling Information**

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *Since there will be instructions for use, please change the "See FDA-approved patient labeling (Medication Guide)" to "See FDA-approved patient labeling (Medication Guide And Instructions For Use)".*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SU-LIN SUN  
05/03/2012

ROBBIN M NIGHSWANDER  
05/07/2012

MEMORANDUM

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

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DATE: May 3, 2012

TO: Director, Investigations Branch  
Florida District Office (FLA-DO)  
555 Winderly Place, Suite 200  
Maitland, FL 32751

Associate Director  
International Operations Drug Group  
Division of Foreign Field Investigations (DFFI)

FROM: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Investigations Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: FY 2012, **High Priority CDER User Fee NDA Pre-Approval  
Data Validation Inspection**, Bioresearch Monitoring,  
Human Drugs, CP 7348.001

RE: NDA 203-993

DRUG: Onfi (clobazam) oral suspension, 2.5 mg/mL

SPONSOR: Lundbeck LLC, USA

Sponsor Address: 4 Parkway North, Suite 200  
Deerfield, IL 60015, USA

Phone: +1-847-262-1066

Fax: +1-847-317-9112

Sponsor Contact: Jenny Swalec, Sr. Director, Regulatory Affairs  
Contact Email: [JSWA@Lundbeck.com](mailto:JSWA@Lundbeck.com)

This memo requests inspections of the clinical and analytical portions of the following bioequivalence study. **At the request of the Review Division, this inspection should be completed before July 30, 2012.**

**Study Number:** 14033A

**Study Title:** Randomized, open-label, two-way crossover study investigating the relative bioavailability of Lu-00-638 (clobazam) oral suspension relative to oral tablets following a single 20 mg dose in healthy subjects

**Clinical Site:** Sea View Research  
3898 NW 7<sup>th</sup> Street  
Miami, FL 33126

**Clinical Investigator:** Axel Juan, MD

The data in the NDA submission should be compared to the original documents at the firms. In addition to the standard investigation involving the source documents, drug accountability, etc., the files of communication during the study conduct should be examined for their content. Please check the batch numbers of the test and reference formulations used in the study with the descriptions in documents submitted to the Agency. The site conducting the above bioequivalence study is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided for subject dosing. **Please confirm whether reserve samples were retained as required by 21 CFR 320.38 and 320.63.** Samples of the test and reference drug formulations should be collected and mailed to the Division of Drug Analysis, St. Louis, MO, for screening at the following address:

Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis (DPA)  
Center for Drug Analysis (HFH-300)  
US Courthouse and Customhouse Bldg  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please obtain a written assurance from the clinical investigator (CI) or the responsible person at the CI's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records.

Please have the records of all subjects in the study audited. The subject records in the submission should be compared to the original documents at the firm. The protocol and actual study conduct, IRB approval, drug accountability, as well as the source documents and case report forms for dosing, clinical and laboratory evaluations, adverse events, concomitant medications, inclusion/exclusion criteria and number of evaluable subjects should be examined. The SOPs for the various procedures need to be scrutinized. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please verify that the subjects were compliant with the trial regimen

and confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR. In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Relevant exhibits should be collected for all findings, including discussion items at closeout, to assess the impact of the findings. Also, please determine if the subjects met the protocol inclusion/exclusion criteria.

**Analytical Site:** H. Lundbeck A.S.,  
Non-Clinical Safety Research  
Department of Bioanalysis

(b) (4)

**Study Director:**

(b) (4)

**Analytical Method:** LC-MS/MS

All pertinent items related to the analytical method for the measurement of clobazam and N-desmethyl-clobazam concentrations should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. The SOP(s) for repeat assays and other relevant procedures must also be scrutinized. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following identification of the investigator background material will be forwarded directly. **A scientist from DBGC, OSI with specialized knowledge may participate in the inspection to provide scientific and technical expertise.** Please contact DBGC upon receipt of this assignment to arrange scheduling of the inspection.

Page 4 - BIMO Assignment, NDA 203-993, Onfi (clobazam) oral  
suspension, 2.5 mg/mL

Headquarters Contact Person: Sripal R. Mada, Ph.D.  
(301)-796-4112

DFFI Contact Person: Arindam Dasgupta, Ph.D.  
(301) 796-3326

cc:

CDER OSI PM TRACK

OSI/DBGC/BB/Haidar/Skelly/Mada/Dasgupta/Dejernet

OND/DNP/Katz/Sun

HFR-SE250/Torres (BIMO), Sinninger/Jackson (DIB)

HFR-SE200/Singleton (DIB)

HFC-130/ORA HQ DFFI IOB BIMO

Draft: SRM 05/02/2012

Edit: MFS 05/02/2012

DSI: 6337; O:\BE\assigns\bio203993.doc

FACTS: 1405758

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SRIPAL R MADA  
05/03/2012

MICHAEL F SKELLY  
05/03/2012  
Skelly signing on behalf of Dr. Haidar