CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202067Orig1s000

OTHER REVIEW(S)

SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 202067
APPLICANT	Lundbeck, Inc.
PRODUCT NAME	ONFI (clobazam)
SUBMISSION TYPE	Original NDA
SUBMISSION DATE	23 Dec 2010
PDUFA DATE	23 Oct 2011
SEALD SIGN-OFF DATE	21 Oct 2011
OND ASSOCIATE DIRECTOR FOR STUDY ENDPOINTS AND LABELING	Laurie Burke

This memo confirms that all Selected Requirements for Prescribing Information (SRPI) criteria are met in the final agreed-upon PI as noted in the SEALD Labeling Review filed 20 Oct 2011. SEALD has no objection to PI approval at this time.

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

/s/

LAURIE B BURKE
10/21/2011

Clobazam - NDA 202-067 - Carcinogenicity study in rats.
PMR #1

PMR Description: A carcinogenicity study of orally administered clobazam in rats.

PMR Schedule Milestones:

Final protocol Submission Date:	05/2013
Study/Clinical trial Completion Date:	03/2016
Final Report Submission Date:	07/2016
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The clinical data demonstrate efficacy for a serious indication (Lennox-Gastaut Syndrome) and warrant approval at this time, and an adequate carcinogenicity study in rat has not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A carcinogenicity study in rat is required to identify an unexpected, serious risk of adverse effects of clobazam, in accordance with guidance set forth in ICH S1B: *Guidance for Industry S1B Testing for Carcinogenicity of Pharmaceuticals July 1997*). The carcinogenicity studies conducted by the sponsor were not adequate, based on numerous deficiencies in conduct and documentation.

Reference ID: 3032252

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A carcinogenicity study of orally administered clobazam in rats.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Reference ID: 3032252

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Reference ID: 3032252

Clobazam - NDA 202-067 - Carcinogenicity study in mice.
PMR #2

PMR Description: A carcinogenicity study of orally administered clobazam in mouse.

PMR Schedule Milestones:		
	Final protocol Submission Date:	08/2013
	Study/Clinical trial Completion Date:	06/2016
	Final Report Submission Date:	10/2016
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The clinical data demonstrate efficacy for a serious indication (Lennox-Gastaut Syndrome) and warrant approval at this time, and an adequate carcinogenicity study in mouse has not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A carcinogenicity study in mouse is required to identify an unexpected, serious risk of adverse effects of clobazam, in accordance with guidance set forth in ICH S1B: *Guidance for Industry S1B Testing for Carcinogenicity of Pharmaceuticals July 1997*). The carcinogenicity studies conducted by the sponsor were not adequate, based on numerous deficiencies in conduct and documentation.

Reference ID: 3032252

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A carcinogenicity study of orally administered clobazam in mouse.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Reference ID: 3032252

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3032252

Clobazam - NDA 202-067 - Fertility and Early Embryonic Development to Implantation Study in Rats

PMR # 3

PMR Description: A fertility and early embryonic development to implantation study in rats

PMR Schedule Milestones:

Final protocol Submission Date:	11/2012
Study/Clinical trial Completion Date:	05/2013
Final Report Submission Date:	10/2013
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The clinical data demonstrate efficacy for a serious indication (Lennox-Gastaut Syndrome) and warrant approval at this time, and an adequate fertility and early embryonic development to implantation study in rat has not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A fertility and early embryonic development to implantation study in rat is required to identify an unexpected, serious risk of adverse effects of clobazam, in accordance with guidance set forth in ICH S5(R2):*Detection of Toxicity to Reproduction for Medicinal Products &Toxicity to Male Fertility* (2005). The fertility and early embryonic development to implantation study in rat conducted by the sponsor was not adequate, based on numerous deficiencies in conduct, design, and documentation.

Reference ID: 3032252

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A fertility and early embryonic development to implantation study in rats.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Reference ID: 3032252

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3032252

Clobazam - NDA 202-067 - Embryo-fetal Development Study in Rats
PMR # 4

PMR Description: An embryo-fetal development study of orally administered clobazam in rats.

PMR Schedule Milestones:		
	Final protocol Submission Date:	09/2012
	Study/Clinical trial Completion Date:	04/2013
	Final Report Submission Date:	08/2013
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The clinical data demonstrate efficacy for a serious indication (Lennox-Gastaut Syndrome) and warrant approval at this time, and an adequate embryo-fetal development study in rat has not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

An embryo-fetal development study in rat is required to identify an unexpected, serious risk of adverse effects of clobazam, in accordance with guidance set forth in ICH S5(R2):*Detection of Toxicity to Reproduction for Medicinal Products &Toxicity to Male Fertility* (2005). The embryo-fetal development studies conducted by the sponsor were not adequate, based on numerous deficiencies in conduct, design, and documentation.

Reference ID: 3032252

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An embryo-fetal development study of orally administered clobazam in rats.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Reference ID: 3032252

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Reference ID: 3032252

Clobazam - NDA 202-067 - Embryo-fetal Development Study in Rabbit
PMR #5

PMR Description: An embryo-fetal development study of orally administered clobazam in rabbits.

PMR Schedule Milestones:

Final protocol Submission Date:	11/2012
Study/Clinical trial Completion Date:	04/2013
Final Report Submission Date:	08/2013
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The clinical data demonstrate efficacy for a serious indication (Lennox-Gastaut Syndrome) and warrant approval at this time, and an adequate embryo-fetal development study in rabbit has not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

An embryo-fetal development study in rabbit is required to identify an unexpected, serious risk of adverse effects of clobazam, in accordance with guidance set forth in ICH S5(R2):*Detection of Toxicity to Reproduction for Medicinal Products &Toxicity to Male Fertility* (2005). The embryo-fetal development studies conducted by the sponsor were not adequate, based on numerous deficiencies in conduct, design, and documentation.

Reference ID: 3032252

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An embryo-fetal development study of orally administered clobazam in rabbits.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Reference ID: 3032252

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3032252

Clobazam - NDA 202-067 - Prenatal and Postnatal Development (including Maternal Function) Study

PMR #6

PMR Description: A prenatal and postnatal development (including maternal function) study of orally administered clobazam in rats

PMR Schedule Milestones:		
	Final protocol Submission Date:	09/2012
	Study/Clinical trial Completion Date:	03/2013
	Final Report Submission Date:	08/2013
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The clinical data demonstrate efficacy for a serious indication (Lennox-Gastaut Syndrome) and warrant approval at this time, and an adequate prenatal and postnatal development (including maternal function) study in rat has not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A prenatal and postnatal development (including maternal function) study in rat is required to identify an unexpected, serious risk of adverse effects of clobazam, in accordance with guidance set forth in ICH S5(R2):*Detection of Toxicity to Reproduction for Medicinal Products &Toxicity to Male Fertility* (2005). The prenatal and postnatal development (including maternal function) study in rat conducted by the sponsor was not adequate, based on numerous deficiencies in conduct, design, and documentation.

Reference ID: 3032252

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prenatal and postnatal development (including maternal function) study of orally administered clobazam in rats.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

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Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

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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.

/s/

SALLY U YASUDA
10/20/2011
Completed PMR templates

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 202067
APPLICANT	Lundbeck, Inc.
PRODUCT NAME	ONFI (clobazam)
TYPE OF APPLICATION	Original NDA
INDICATION	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome
TYPE OF PRODUCT	Benzodiazepine
OFFICE/DIVISION	ODEI/DNP
SUBMISSION DATE	December 23, 2010
PDUFA DATE	October 23, 2011
SEALD REVIEW DATE	October 20, 2011
SEALD LABELING REVIEWER	Eric Brodsky, M.D.

The following checked Selected Requirements for Prescribing Information (SRPI) items have been reviewed for this original NDA application. These 46 specific SRPI items assess mostly labeling format according to regulations and labeling guidances. This reviewer actively engaged with the review division on the ONFI label. Based on this SRPI review, there are **NO** outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
  - ☐ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and Table of Contents (TOC).
  - ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
  - ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state “None”)
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

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- **Highlights Limitation Statement**
  - ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: "**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)**."

- **Product Title**
  - ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded**.
  - ☐ Summary of the warning must not exceed a length of 20 lines.
  - ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").
  - ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."
  - ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.
  - ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - ☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

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- **Indications and Usage**

  ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

  ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”

  ☐ All contraindications listed in the FPI must also be listed in HL.

  ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

  ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

  ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

  ☐ For drug products other than vaccines, the verbatim **bolded** statement, “**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**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

  ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**.

- **Revision Date**

  ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection 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."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

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- **Adverse Reactions**

  ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.

  ☐ For the "Clinical Trials Experience" subsection, 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."

  ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

  > "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."

- **Use in Specific Populations**

  ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

  ☐ This section is required and cannot be omitted.

  ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:

  - "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)"

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/s/

ERIC R BRODSKY
10/20/2011

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 # 202067 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Onfi Established/Proper Name: clobazam Dosage Form: tablet Strengths: 5mg, 10mg, and 20mg		
Applicant: Lundbeck, Inc Agent for Applicant (if applicable): Jenny Swalec		
Date of Application: 12/23/2010 Date of Receipt: 12/23/2010 Date clock started after UN: N/A		
PDUFA Goal Date: 10/23/2011	Action Goal Date (if different): 10/21/2011	
Filing Date: 02/21/2011	Date of Filing Meeting: 01/26/2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome in patients greater than or equal to 2 years of age		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults*** ***N/A***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

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☐ Fast Track ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 070125	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	x			
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)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	S			Standard review
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		x		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

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User Fee Status ***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.***	Payment for this application: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			x	
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)].**			x	
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)]?** ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*			x	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:			x	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***	x			Rufinamide Felbamate Lamotrigine Topiramate

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If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		x		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	x			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		x		
If yes, 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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

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

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**x**	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	x			
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	x			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	x			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	s			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	s			

Reference ID: 3032372

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) 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…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	x			

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :	**x**			

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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 & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		x		Orphan designation
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		x		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

Reference ID: 3032372

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			x	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***			x	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				n/a
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	x			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***	x			Sponsor agreed no REMS required on 04/27/2011 based on the Agency's recommendation.
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	x			
Is the PI submitted in PLR format?[4]	x			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Reference ID: 3032372

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			x	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	x			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x			
OTC Labeling	**☒ Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			x	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			x	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			x	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	x			QT-IRT Carcinogenicity STAT
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** May 9, 2007 ***If yes, distribute minutes before filing meeting***	x			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** August 31, 2010	x			

Reference ID: 3032372

If yes, distribute minutes before filing meeting				
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		x		

Reference ID: 3032372

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 26, 2011

NDA #: 202067

PROPRIETARY NAME: Onfi

ESTABLISHED/PROPER NAME: clobazam

DOSAGE FORM/STRENGTH: 5mg, 10mg, and 20mg

APPLICANT: Lundbeck Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): adjunctive treatment of seizures associated with Lennox Gastaut syndrome (LGS) in patient ≥ 2 years of age

BACKGROUND:
Clobazam is a 1,5-benzodiazepine with anti-convulsant, sedative, anxiolytic, and muscle-relaxant properties. Lundbeck Inc. (formerly Ovation Pharmaceuticals) acquired regulatory, distribution, and marketing rights for clobazam in the US, Canada, and Mexico from sanofi-aventis in March 2004. Lundbeck is the marketing authorization (MA) holder in Canada (b) (4)
(b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Su-Lin Sun	Y
	OSE:	Laurie Kelley	N
Cross-Discipline Team Leader (CDTL)	Norman Hershkowitz		Y
Clinical	Reviewer:	Philip Sheridan	Y
	TL:	Norman Hershkowitz	Y

Reference ID: 3032372

Clinical Pharmacology	Reviewer:	Seongeun Cho till 6/27/11 Ta-Chien Wu after 6/27/11	Y N
	TL:	Angela Men	Y
Biostatistics	Reviewer:	Ohidul Siddiqui	Y
	TL:	Kun Jin	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Edward Fisher	Y
	TL:	Lois Freed	Y
Statistics (carcinogenicity)	Reviewer:	Min Min	N
	TL:	Karl Lin	N
Product Quality (CMC) Facility Review/Inspection	Reviewer:	Akm Khairuzzaman	Y
	TL:	Martha Heimann	Y
Biopharmaceutics	Reviewer:	Akm Khairuzzaman	Y
	TL:	Angelica Dorantes	Y
Safety Review	Reviewer:	Gerard Boehm	Y
	TL:	Sally Yasuda	Y
OSE/DMEPA (proprietary name)	Reviewer:	Lubna Merchant till 10/11 Reasol Agustin after 10/11	Y N
	TL:	Melina Griffs till 10/11 Lubna Merchant after 10/11	Y
OSE/DRISK	Reviewer:	Twanda Scales	Y
	TL:	Melissa Hulett	Y
OC/DCRMS (REMS)	Reviewer:	Kendra Biddick	Y
	TL:	NA	N

Reference ID: 3032372

Bioresearch Monitoring (DSI)	Reviewer:	Antoine El-Hage	Y
	TL:	Tejashri Purohit-Sheth	Y
Controlled Substance Staff (CSS)	Reviewer:	Alicja Lerner	Y
	TL:	Michael Klein	Y
DDMAC (PI) review	Quynh-Van Tran		Y
DDMAC (MG) review	Sharon Watson		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable***	☐ YES Date if known: ☒ NO ☐ To be determined o Reason: ***the application did not raise significant safety and efficacy issues***

Reference ID: 3032372

○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	
• Abuse Liability/Potential **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☐ Not Applicable ☐ YES ☒ NO
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Reference ID: 3032372

PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ ☐ YES ☐ NO ☒ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ellis Unger, MD **21st Century Review Milestones** **74 day letter by March 7, 2011, Midcycle meeting on5/26/11, primary review done by 08/28/11, secondary review by 09/04/11; Wrap up meeting on 08/25/11; send proposed labeling/PMC/PMR to applicant by 09/23/11**	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:

Reference ID: 3032372

☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	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).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • 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) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct labeling review and include labeling issues in the 74-day letter
☐	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 (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

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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

Reference ID: 3032372

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/

SU-LIN SUN
10/20/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Direct-to-Consumer Promotion

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

Memorandum

Date: October 6, 2011

To: Su-Lin Sun, Pharm.D.
Senior Regulatory Project Manager
Division of Neurology Products (DNP)

From: LCDR Sharon M. Watson, Pharm.D., USPHS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP), Division of Direct-to-Consumer Promotion [formerly known as Division of Drug Marketing, Advertising, and Communications (DDMAC)]

Subject: OPDP Comments on draft Medication Guide (Med Guide) for ONFI (clobazam) tablets, for oral use

NDA 202067

This consult is in response to DNP's request for OPDP's review of the proposed Med Guide for ONFI (clozabam) tablets. We appreciate the opportunity to provide comments on the Med Guide. Please see attached Med Guide with our comments incorporated therein. The version reviewed is the October 5, 2011, Patient Labeling Review provided by the Office of Medication Error Prevention and Risk Management, Division of Risk Management. Comments are based on the October 3, 2011, proposed draft product labeling (PI) submitted by the sponsor.

If you have any questions, please contact Sharon Watson, (301) 796-3991, or sharon.watson@fda.hhs.gov.

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/s/

SHARON M WATSON
10/06/2011

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

PATIENT LABELING REVIEW

Date:	**October 5, 2011**
To:	Russell Katz, M.D., Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management** Melissa Hulett, RN, BSN, MSBA Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management**
From:	Twanda Scales, RN, BEN, MSN/Ed. Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name (established name):	ONFI (clobazam)
Dosage Form and Route:	Tablets
Application Type/Number:	NDA 202067
Applicant:	Lundback, Inc.
OSE RCM #:	2011-188

Reference ID: 3024926

1 INTRODUCTION

On December 23, 2010 the Applicant submitted an Original New Drug Application seeking approval for the adjunctive treatment of seizures associated with Lennox Gastaut syndrome (LGS) in patients ≥ 2 years of age.

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for ONFI (clobazam).

2 MATERIAL REVIEWED

- Draft ONFI (clobazam) Medication Guide (MG) received on January 27, 2011 and revised by the review division throughout the review cycle and sent to DRISK on September 26, 2011.
- Draft Prescribing Information (PI) received January 27, 2011 revised by the Review Division throughout the current review cycle and received by DRISK on September 28, 2011.
- Approved Klonopin (clonazepam) comparator labeling dated September 1, 2010.

3 REVIEW METHODS

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 we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

Reference ID: 3024926

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
10/05/2011

LASHAWN M GRIFFITHS
10/05/2011

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

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

Memorandum

Date: September 28, 2011

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, Division of Professional Promotion [formerly known as Division of Drug Marketing, Advertising, and Communications (DDMAC)]

Subject: DDMAC Comments on draft Prescribing Information (PI) for ONFI (clobazam) tablets, for oral use

NDA 202067

This consult is in response to DNP's request for DDMAC's review of the proposed PI for ONFI (clozabam) tablets. We appreciate the opportunity to provide comments on the PI. Please see attached PI with our comments incorporated therein.

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/

QUYNH-VAN TRAN
09/28/2011

Executive CAC
Date of Meeting: September 20, 2011

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
William Taylor, Ph.D., DTOP, Alternate Member
Lois Freed, Ph.D., DNP, Supervisor
Ed Fisher, Ph.D., DNP, Presenting Reviewer

Author of Draft: Ed Fisher

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 202-067
Drug Name: Onfi (clobazam) Tablets
Sponsor: Lundbeck

Background:

Mouse Carcinogenicity

Clobazam (CLB) was administered in the diet to CD-1 mice at concentrations targeted to result in doses of 0, 4, 20, or 100 mg/kg for 80 weeks. No justification for dose selection was provided in the study report. According to the sponsor, the HD was "33% to 40% of the lowest single oral lethal dose in mice, and on a body surface area (mg/m^2) basis, was 8- to 12-times the maximum dose studied in Phase II/III controlled trials [10-times MRHD]." Due to a high rate of mortality, attributed primarily to injury associated with severe fighting, 42 HD males (report says 43, but one animal was apparently double counted) were replaced during the first 6 weeks of the study. Nine weeks after study initiation an additional 42 males were added and received 100 mg/kg/day for 80 weeks. These animals were said to be several days younger at initiation than the original animals, and apparently displayed fewer behavioral abnormalities on initiation of treatment, fought less, and as a result had improved survival relative to the original group of HD males, none of which survived to study termination. Although the sponsor attributed the HD mortality to fighting, females also showed a dose-related decrease in survival. Body weight was unaffected by treatment in either sex. A dose-related increase in the incidence of hepatocellular adenoma was observed in males when the added group of HD males was used (1/60, 3/60, 3/60, and 5/42 in C, LD, MD, and HD, respectively); however, based on FDA's statistical analysis, the finding was not statistically significant. Hepatocellular carcinomas were not diagnosed in the male mice.

Sex	Organ Name	Tumor Name	Cont 0mg N=60	Low 4mg N=60	Med 200mg N=60	High 100mg N=42	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Male	liver	adenoma, hepatocellu	1	3	3	5	0.020	0.337	0.317	0.041

Among HD female mice, there were fewer tumor-bearing mice than in controls due to a lower frequency of all tumors except pulmonary adenoma in this group. According to the report, the lower tumor incidences were due to the fact that mortality was significantly increased in both sexes at the HD (original HD males), so that the number of treatment weeks was too low for the full expression of the normal tumor frequency to occur, especially lymphoma.

In addition to its confounding effect on mortality, group housing would affect the reliability of dietary dosing, since food consumption was calculated per cage. This combined with the lack of TK data and failure to demonstrate stability of the drug in the diet makes the accuracy of dosing very questionable.

Because of the age of the mouse and rat carcinogenicity studies (final reports for these studies were issued in October, 1979, shortly after GLP regulations were issued [June 1979]), the sponsor provided an impact analysis of the deviations from GLP. According to the sponsor, "both studies were conducted by a reputable contract research laboratory in accordance with the state of the science at that time and are considered to represent scientifically sound and accurate presentations of valid data." The following deviations from the current documentation and observational requirements were noted: study initiation date not provided; test article identity, confirmation of stability not performed; test article lots and expiration dates not provided; reserve sample was not taken; there was no indication of a Quality Assurance (QA) oversight; there was no QA statement; report not signed by study director; study protocol not available; protocol compliance cannot be assessed; method of animal identification was not provided; no description of circumstances that may have affected data quality or integrity; and no information regarding the location or archived specimens and data along with the final report.

In addition, due to the legacy nature of the studies, electronic tumor datasets (tumor.xpt) for these studies were not available and had to be created by the sponsor. Raw histopathology data from the respective appendices of each study report were data entered to create the tumor dataset for the CLB NDA. A description on how the mouse and rat tumor datasets were created and an updated statistical evaluation of survival and tumor incidence data from both studies using these datasets were provided in two additional reports. Both of these reports note the following:

> The study report indicates that an extensive list of organs from all animals was examined at necropsy and saved in fixative. It further indicates that selected organs from all animals were examined microscopically while all other organs were only examined microscopically in a portion of the animals. The individual animal pathology tables in the study report only present organs in which macroscopic or microscopic findings were observed or organs that were missing or unsuitable for microscopic evaluation. For any organ that was present but for

Reference ID: 3021630

which no macro- or microscopic finding was observed, there is no statement in the report that the organ was examined or was without findings. Therefore, it is not possible to definitively determine the number and type of organs examined microscopically in each animal.

The report states that all organs were examined macroscopically at necropsy and any organ with a macroscopic finding that was considered to potentially represent a neoplastic change was saved in fixative for microscopic examination. Therefore, it was assumed that any organ for which macroscopic and microscopic findings were not reported had no tumor. Although this assumption
may not be true in all cases, it was considered unlikely that significant numbers of tumors could have been present in these organs that appeared macroscopically normal at necropsy.

This and the reduced number of tissues included originally (28 vs 50+ recommended) are major deficiencies impacting the adequacy of the study. It is not clear that adequate numbers of animals were exposed for an adequate length of time or that an adequate number of tissues in an adequate number of animals was examined histopathologically. Other problems include the high rate of mortality in the mouse study, such that the FDA statistician questioned the validity of the study; the uncertain contribution of age and the role fighting played in the mortality in male mice; questions about the comparability of the second HD male group; the lack of justification for dose selection; uncertainty about the accuracy of dosing given dietary administration with group housing, no drug stability, and no TK; and the deviations from the current documentation and observational requirements noted above.

Rat Carcinogenicity

CLB was administered in the diet to Sprague-Dawley rats at doses of 0, 4, 20 or 100 mg/kg/day for 104 weeks. Treatment did not induce any notable clinical observations or drug-related changes in mortality, although overall survival was low. A dose-related increased incidence of thyroid follicular cell adenomas was seen in male rats that was statistically significant at the HD in both the sponsor's and FDA's analyses. Thyroid follicular cell carcinomas were not diagnosed in the male rats. The types, incidences, and distribution across treatment groups of other neoplastic changes, including malignant neoplasms, did not appear to be affected by treatment. The results of two mechanistic studies conducted in rats indicated that CLB can alter the pituitary-thyroid axis, presumably through enzyme induction, leading to changes in thyroid function and size in the rat.

Organ Name	Tumor Name	Cont N=60	Low N=60	Med N=60	High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H	
THYROID	ADENOMA, FOLLICULAR	3	2	5	15	0.000	0.803	0.355	0.002	Male

Reference ID: 3021630

Although there was no justification of dose selection in the report, doses appeared adequate based on BW effects and survival. However, as in the mouse study, the potential effect of group housing on the accuracy of dietary dosing combined with the lack of TK and stability data present a serious problem. And as seen in the mouse study, there were significant deficiencies in the provision and/or reporting of data. The following deviations from the current requirements were noted: study initiation date not provided; test article identity, confirmation of stability not performed; test article lots and expiration dates not provided; reserve sample was not taken; there was no indication of a Quality Assurance (QA) oversight; there was no QA statement; report not signed by study director; study protocol not available; protocol compliance cannot be assessed; method of animal identification was not provided; no description of circumstances that may have affected data quality or integrity; and no information regarding the location or archived specimens and data along with the final report.

The rat tumor dataset report contained the same statement that "it is not possible to definitively determine the number and type of organs examined microscopically in each animal" and made the same assumption that "any organ for which macroscopic and microscopic findings were not reported had no tumor" as the mouse study report. This lack of documentation and the limited number of tissues included in the protocol constitute major deficiencies impacting the adequacy of the rat study.

Executive CAC Recommendations and Conclusions:

Mouse:

> The Committee found the study to be inadequate, noting replacement of HD animals at 6 and 9 weeks (with younger animals), missing histopathology (inability to determine the number of tissues examined and the number of animals examined for histopathology), group housing during a feed study, and other reasons detailed above.
>
> The Committee found no statistically significant drug related neoplasms in the study, as conducted.

Rat:

> The Committee found the study to be inadequate for the reasons detailed above but concluded that the thyroid follicular cell adenomas in HD males were drug related.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

Reference ID: 3021630

/DNP Division File
/LFreed, DNP
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ADELE S SEIFRIED
09/28/2011

DAVID JACOBSON KRAM
09/28/2011

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 16, 2011

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 202-067**
Product Name: Onfi (Clobazam)
Indication: Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients > 2 years of age
Dosages: 0.25, 0.5 and 1.0 mg/kg/day tablets for oral administration: tablets 5, 10, and 20 mg
Sponsor: Lundbeck Inc.

Materials reviewed: NDA (Dec 23, 2010) is located in EDR \\cdsesub5\EVSPROD\NDA202067\202067.ENX;
EOP2 Meeting Minutes (May 9, 2007) http://darrts.fda.gov:7777/darrts/ViewDocument?documentId=090140af800bf2d2
Previous IND 70,125
CSS request consult: Aug 24, 2010

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Reference ID: 3016525

SUMMARY

A. BACKGROUND

This memorandum responds to the DNP consult regarding the evaluation of abuse potential of Onfi (clobazam). 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 Dec 23, 2010, Lundbeck Inc. (formerly Ovation Pharmaceuticals) filed NDA 202-167 for the indication of the 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 temporarily listed in Schedule IV of the Controlled Substances Act (CSA) based on international scheduling in the Convention on Psychotropic Substances in 1984 (49 FR 39307, 1084). Upon approval, CSS will provide an 8 Factor Analysis to the Drug Enforcement Administration (DEA) in order to begin the process to permanently schedule clobazam in Schedule IV under the CSA.

CSS consulted the Office of Surveillance and Epidemiology (OSE) to review foreign databases regarding the abuse, misuse and overdose associated with clobazam and to include also reports of psychiatric adverse events, suicidal behavior and deaths.

B. CONCLUSIONS

1. Clobazam is a benzodiazepine and listed temporarily in Schedule IV of the Controlled Substances Act (CSA).

2. Clobazam has a benzodiazepine chemical structure. In receptor binding studies, clobazam and its main active metabolite showed significant binding at the benzodiazepine site of the $GABA_A$ receptor (see Discussion, Chemistry, and Pharmacology of drug substance and active metabolites, page 4 and following).

3. In preclinical studies (performed by the sponsor and reported in published papers) clobazam elicits in animals decreased motor activity, muscle relaxation, impaired righting reflex, limited use of hindlimbs, and ataxia. Clobazam also elicits anxiolytic and anti-aggressive effects, as do other benzodiazepine substances (see Discussion).

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4. In clinical trials in patients with anxiety disorders, clobazam was frequently compared with benzodiazepines, in particular with diazepam. Clobazam showed similar anxiolytic effects as diazepam. The median half-lives of clobazam and N-desmethyl-clobazam (N-CLB) were estimated to be 36 hours and 79 hours, respectively. Peak serum concentrations of clobazam after oral administration, is ~244 ng/ml after 20 mg. After repeated doses, steady-state concentration of unchanged clobazam is achieved within 1 week. At steady-state, N-CLB plasma exposures (AUC) are approximately 3 times higher than those of clobazam. Following clobazam twice-daily administration to steady-state, N-CLB accumulates approximately 20 times.

5. In the clinical trials performed by the sponsor and according to the scientific literature, clobazam elicited development of dependency and tolerance; in addition, cases of overdose were noted.

   A. Abrupt discontinuation of the drug causes withdrawal symptoms (see Discussion, Prospective evaluation of physical dependence in phase 1 and 2/3 studies, page 13).

   B. Withdrawal reactions to clobazam are also reported in the scientific literature (Petursson and Lader, 1981) (see Discussion, Scientific literature-withdrawal reactions, page 15).

   C. There were a number of overdose cases noted by the sponsor, and captured in the WHO database (see Discussion, Safety profile-postmarketing data, page 14 and Epidemiology data bases related to abuse of product, page 15)

6. Adverse events profile in clinical trials shows the following: somnolence, lethargy, sedation, fatigue, ataxia, and dizziness, all of which are also associated with other benzodiazepine substances.

7. The postmarketing studies describe the following nervous and psychiatric adverse events: somnolence, sedation, depressed level of consciousness, dizziness, memory loss, ataxia, and substance related disorders: drug dependence, drug abuse, and withdrawal syndrome.

8. Co-administration of clobazam with alcohol increases the maximum exposure of clobazam by 50%. The draft label contains a warning language.

9. Co-administration of clobazam with dextromethorphan (CYP2D6 substrate) leads to increases of 90% in AUC and 59% in C_{max} values for dextromethorphan (and possibly other opiates, as well) in CYP2D6 extensive metabolizers, which is consistent with weak inhibition of the CYP2D6 isozyme.

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C. RECOMMENDATIONS

1. Clobazam should be recommended for permanent control in Schedule IV of the CSA, because of its similarity in pharmacology and abuse potential to other benzodiazepines that are listed in Schedule IV.

2. The label should state that clobazam should not be taken concomitantly with dextromethorphan (and possibly other opiates) because it leads to increases of 90% in AUC and 59% in C_{max} values for dextromethorphan (and possibly other opiates) in CYP2D6 extensive metabolizers

3. In addition, the label should include information with regard to the abuse and dependence potential of clobazam as similar to other benzodiazepines that are approved for medical use and listed in Schedule IV of the CSA.

4. The container closure system should be child proof, and the container with the medication should be stored in the place where the child can not reach it.

II. DISCUSSION

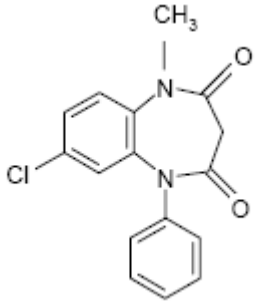
A. Chemistry

1. Product description

The final commercial product is an (b) (4) tablet and contains 5, 10, or 20 mg clobazam in proportionally-sized tablet. All tablets will be debossed on one side with the letters "LU" and the other side with numbers "5", "10", or "20" to identify the tablets as being 5 mg, 10 mg or 20 mg clobazam tablets, respectively. Tablets also contain inactive ingredients: corn starch, lactose monohydrate, magnesium stearate, silicon dioxide, and talc (Table 1. Mod 2.3.P, NDA)

The molecular formula of clobazam is $C_{16}H_{13}O_2N_2Cl$ and the molecular weight is 300.7. There are no chiral centers in clobazam. Clobazam is a white or almost white, crystalline powder which is freely soluble in methylene chloride, slightly soluble in water, and sparingly soluble in ethanol. The melting point range of clobazam is from 182ºC to 185ºC. The Chemical Abstract Service chemical identification number is CAS # 22316-47-8.

Structural formula:



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2. Potential drug isomers

As clobazam has no chiral centers, it does not have stereoisomers.

B. Pharmacology of drug substance and active metabolites

Clobazam is a 1,5–benzodiazepine with sedative, anxiolytic, muscle relaxant, and anticonvulsant properties.
The diazepine ring of clobazam has nitrogen atoms at the 1 and 5 positions (as opposed to the typical 1 and 4 benzodiazepine substances with anxiolytic properties). Clobazam is believed to be an allosteric modulator of the effects of γ-aminobutyric acid (GABA) at the $GABA_A$ receptor, resulting in an increase in chloride ion current.

Clobazam has two major metabolites: N-desmethyl-clobazam (N-CLB) and 4'-hydroxyclobazam, the former of which is active.

The primary pharmacodynamic activity of N-CLB was evaluated in selected studies indicative of anxiolytic action, and results indicate that like clobazam, N-CLB is active, though not as potent as clobazam.

In vitro studies

- Receptor binding studies

The sponsor performed two studies to evaluate receptor binding, using an assay of 78 receptors. One study examined clobazam and the other examined its major active metabolite, N-desmethylclobazam (N-CLB).

A. *In vitro receptor binding assays for clobazam (Study ONVC-9035)*

I*n vitro* receptor binding assays showed significant binding of clobazam at the central benzodiazepine receptor with 98% binding inhibition (IC50 = 0.43 μM; Ki = 0.36 μM), the peripheral benzodiazepine receptor with 60% binding inhibition (IC50 = 5.9 μM; Ki = 5.3 μM), and the γ-aminobutyric acid (GABA)-gated chloride channel with 47% binding inhibition (IC50 = 0.11 μM; Ki = 0.095 μM). Also observed were increased to 29% binding inhibition at the opioid kappa receptor and 24% at the melatonin MT1 receptor.

B. *In vitro receptor binding assays for N-desmethylclobazam (#ONVC-9048)*

In vitro receptor binding assays showed significant binding of N-CLB mainly at the central benzodiazepine BZD receptor, with 82% binding inhibition (IC50 = 0.39 μM; Ki = 0.33 μM), the peripheral benzodiazepine BZD receptor 64% binding inhibition (IC50 = 2.8 μM; Ki = 2.5 μM), and the GABA-gated chloride channel, 59% binding inhibition (IC50 = 1.8 μM; Ki =1.5 μM). Also observed were increased to 40% binding inhibition at the cannabinoid CB1 receptor, to 32% at the serotonin 5-HT7 receptor, to 28% at the serotonin 5-HT2B receptor, to 27% at the dopamine transporter, to 29% at the adenosine A3 receptor, and to 24% at the melatonin MT1 receptor.

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These data suggest that 1) both clobazam and its active metabolite N-CLB have strong influence at the GABAA receptor, 2) Clobazam and N-CLB may affect other abuse related receptors including those of cannabinoid, opioid, dopaminergic and serotonergic systems.

2. **Safety pharmacology findings**

Safety pharmacology studies to assess effects of clobazam on the central nervous system (CNS) have not been conducted. The only study which examined CNS effects was the juvenile rat toxicity study (Summary 2.6.7, Table 15, OVNC-9005); otherwise the sponsor relies on the results of primary and secondary pharmacodynamic non-clinical studies, and clinical studies.

- General behavioral responses

3. ***Animal behavioral studies***

Study in Juvenile Animals (OVNC-9005) - Oral (Gavage) Repeated-Dose Toxicity Study of Clobazam in Rats

Rats received a single oral dose of clobazam daily at 0, 4, 36, and 120 mg/kg daily from Postnatal Day 14 to Postnatal Day 48, 49, or 53; tolerance, behavioral parameters, and reproductive performance were assessed. Behavioral observations included: 1) evaluation of motor activity, 2) acoustic startle habituation, 3) Morris water maze test and 4) assessment of the multiple behavioral parameters and clinical signs.

During the study there were no clobazam-related deaths. Mean body weight and body weight gain during the treatment period in females at ≥36 mg/kg/day were decreased 6% to 15%. Regarding the behavior decreased motor activity, impaired righting reflex, limited use of hindlimbs, ataxia, and repetitive licking were observed mainly at ≥36 mg/kg/day during the first two weeks of dosing. However, decreased motor activity was also observed in three male rats in the 4 mg/kg/day dosage group and one female rat in this dosage group had decreased motor activity and impaired righting reflex. At dose 120 mg/kg/day, motor activity was increased in females. Morris water maze testing showed increased time to reach the platform in the first of 3 consecutive daily sessions in females at 120 mg/kg/day. Acoustic startle habituation was unaffected by dosages of clobazam as high as 120 mg/kg/day.

- Self administration studies
- Self administration study in monkeys (# LNCT-027)

The study was performed in 1975 to evaluate abuse potential of clobazam.
Design: 25 Drug-naïve rhesus monkeys (M/F) were subjected to the self-administration of morphine HCl at 0.05 mg/kg through the indwelling jugular vein catheter through which morphine was delivered after pressing a lever. The monkeys were allowed to use self-administration for 8 h daily, and were considered to be morphine dependent if they self-injected more than 30 individual doses within the first 3 h of a daily injection period. During next phases of increasing dependence, monkeys had to change the ratio of lever presses from 1:1 to 10:1. After completing the dependence phase, for the next 3 days monkeys were given only saline to inject. Then, for the following 3 days, clobazam was made available in the doses 0.025, 0.05, and 0.1 mg/kg, each dose in a group of 5 animals. Codeine HCl (0.05 mg/kg) was used as a positive control. Subsequently, for the next 3 days morphine was provided for reinjection.

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Results: Dependent monkeys made ~60-70 injections during the first 3 hrs of injection period, compared to baseline of 14.1+/- 5.7 injections. During the saline period, 18 to 23 injections were made, whereas during the test period with clobazam at doses 0.025, 0.05, and 0.1 mg/kg monkeys made 18.1+/- 6.7; 19.9+/- 7.3; and 13.5+/-6.1 injections, respectively; codeine would produce 66.3+/-21.7 injections.

Comments:
Inadequate information was provided in this brief study summary regarding whether monkeys who had been exposed to morphine in the self-administration paradigm had developed physical dependence to the opioid at the time of clobazam testing. Thus, the negative results obtained when clobazam was substituted for morphine may be the result of animals experiencing opioid withdrawal. Additionally, self-administration of codeine may be explained as providing relief of opioid withdrawal.

C. **Clinical pharmacology**

1. ***Absorption***

Clobazam is rapidly and extensively absorbed after oral administration. Tmax ranges from 0.5 to 4 hours. The administration of clobazam with food does not affect the overall extent of absorption (AUC), but Cmax is reduced by 22% relative to the fasting state, food also slows the rate of absorption. Peak plasma levels (Cmax) and the AUC are both dose proportional for doses of 10-40 mg. The pharmacokinetics of clobazam was assessed to be linear for doses up to 160 mg/day. Clobazam accumulates approximately 2-3 times at steady-state.

Clobazam is lipophilic and distributes rapidly throughout the body. The apparent volume of distribution at steady-state is approximately 102 liters (L). The *in vitro* plasma protein binding of clobazam and its primary metabolite N-CLB is similar, ranging from 78% to 89%, and is concentration independent. The *ex vivo* plasma protein binding of clobazam and N-CLB is approximately 90% for both compounds.

2. ***Metabolism***

- Characterize active parent drug and active metabolites

Clobazam is extensively metabolized in the liver primarily by cytochrome P450 3A4 (CYP3A4) and to a lesser extent by CYP2C19 and CYP2B6. N-Demethylation leads to formation of the main pharmacologically active metabolite N-CLB, detected in human plasma and greater than 10% of parent drug. In total, 25 metabolites have been identified in humans. At steady-state, N-CLB plasma exposures (AUC) are approximately 3 times greater than those of clobazam. Following clobazam twice-daily (BID) administration to steady-state, N-CLB accumulates approximately 20 times.

In vitro results show that both clobazam and N-CLB are substrates of permeability glycoprotein (P-gp) –mediated transport and are not inhibitors of P-gp.

3. ***Elimination***

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Clobazam metabolic products are mainly excreted through the kidney (less than 1% as unchanged clobazam and less than 10% as N-CLB) with 82% of the radioactivity after a single dose of 14C-clobazam recovered in the urine and 11% in feces.

4. ***Pharmacokinetics / pharmacodynamics parameters of parent drug & active metabolites***

- Cmax, Tmax, Emax

The median half-lives of clobazam and N-CLB were estimated to be 36 hours and 79 hours, respectively, and the apparent plasma clearance of clobazam was 2.5 L/hour. Tmax ranges from 0.5 to 4 hours. The pharmacokinetics of clobazam was assessed to be linear for doses up to 160 mg/day. Peak serum concentrations of unchanged drug after oral administration, are about 244 ng/ml after 20 mg, 430 ng/ml after 30 mg and 527 ng/ml after 40 mg [1]. After repeated doses, steady-state concentration of unchanged clobazam is achieved within 1 week. Clobazam accumulates approximately 2-3 times at steady-state. Steady-state levels of N-CLB appear to be about 8 times greater than those of the unchanged drug

- Drug/product interactions (alcohol, drugs, food, dietary supplements, etc.)

Alcohol increased the maximum exposure of clobazam by 50% [2]. The effect of alcohol on the bioavailability of clobazam was shown in the study where eight healthy male volunteers received either: a) clobazam 20 mg; (b) placebo; (c) alcohol + placebo; and (d) alcohol + clobazam 20 mg. Alcohol was administered orally in quantities individually calculated to yield serum alcohol concentrations of about 1000 μg/ml. Blood samples were obtained before and 50, 100, 160, 220, 280, 340 and 1440 min after administration. The study showed that serum clobazam levels were higher after combined administration of clobazam and alcohol than after clobazam alone. The peak serum levels after clobazam + alcohol were 388.75 + 157.16 ng/ml and were significantly higher than after clobazam alone: 243.75 + 86.67 ng/ml (P> 0.05). These findings demonstrate that there is a clear pharmacokinetic interaction, in that alcohol administered with clobazam results in enhanced clobazam bioavailability.

Dextromethorphan (CYP2D6 substrate) coadministered with clobazam led to increases of 90% in AUC and 59% in Cmax values for dextromethorphan in CYP2D6 extensive metabolizers, which is consistent with weak inhibition of the CYP2D6 isozyme.

Food effects when administered with crushed tablets were assessed (OV-1018). The design was a single-dose, 2-way crossover, single-center, randomized, open-label study. The primary goal was to assess the effects of single oral doses of clobazam 20 mg (4 × 5 mg tablets or 1 × 20 mg tablet) administered as crushed tablets with applesauce on the pharmacokinetics and oral bioavailability of clobazam, and to assess the effects of a high-fat meal on the pharmacokinetics and oral bioavailability of a single intact 20 mg oral dose of clobazam (1 × 20 mg tablet) in a

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[1] Brogden 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.

[2] Taeuber K, Badian M, Brettel HF, Royen T, Rupp W, Sittig W, Uihlein M. Kinetic and dynamic interaction of clobazam and alcohol. Br J Clin Pharmacol. 1979;7 Suppl 1:91S-97S

Reference ID: 3016525

group of 48 adult men (33) and women (15). Additionally, safety and tolerability of administered medication with these both food schedules was evaluated. The study showed reduction of clobazam Cmax of 22% when administered with high-fat meal relative to fasting state. Also the median Tmax was delayed by 1 hour when clobazam was administered with a high-fat meal. Nevertheless, the sponsor stated that there was no effect on the extent of absorption as measured by AUC and therefore, clobazam can be given without regard to meals.

- Pharmacogenetic considerations (metabolizer status)

At steady-state, the systemic exposure of clobazam is similar between CYP2C19 poor and extensive metabolizers, but CYP2C19 poor metabolizers have approximately a 5-fold higher plasma exposure of N-CLB as compared to that of extensive metabolizers.

Development of tolerance in humans

The scientific literature in the public domain provides evidence for rapid development of tolerance to the anti-epileptic effect of clobazam in noncontrolled studies. Tolerance was noted days following the start of therapy [3] and as late as 3 years.[4] In most published studies, the subjects who demonstrate tolerance to clobazam do so within the first 3-4 months of therapy.

D. **Clinical Studies**

The NDA ISS section summarizes safety data from 56 clinical studies submitted by the sponsor:

• Phase 1: 8 pharmacology studies in healthy adults (conducted by Lundbeck)
• Phase 2 and 3 LGS patients: 3 studies (conducted by Lundbeck)
  • Phase 3, Study OV-1012, pivotal study, randomized, double-blind, placebo-controlled, parallel-group in patients with LGS
  • Phase 2, (Study OV-1002, supportive study, randomized, double-blind, dose-ranging, parallel-group in patients with LGS
  • Phase 2/3, ongoing, uncontrolled, open-label extension for subjects who participated in Studies OV-1002 and OV-1012 (Study OV-1004)

• Legacy Epilepsy Study 301 (conducted by the prior sponsor in pediatric subjects with epilepsy)
• Legacy Psychiatry Studies: 44 Legacy Psychiatry Studies (conducted by the prior sponsor) comprise 35 controlled studies and 9 uncontrolled studies. These studies were primarily conducted in adult subjects with anxiety or neuroses and one study was conducted in pediatric subjects with various psychiatric disorders.

44 studies:
N=1484 subjects
• 8 controlled studies (US and Canada): N=203
• 18 controlled studies (Rest of World): N=395
• 9 controlled studies (non-CRF): N=615
• 5 uncontrolled studies (CRF): N=200
• 4 uncontrolled studies (non-CRF): N=71

[3] Schmidt D, Rohde M, Wolf P, Roeder-Wanner U. Clobazam for refractory focal epilepsy. A controlled trial. Arch Neurol 1986;43:824-826.
[4] Singh A, Guberman AH, Boisvert D. Clobazam in long-term epilepsy treatment: sustained responders versus those developing tolerance. Epilepsia 1995;36(8):798-803.

Reference ID: 3016525

No human abuse potential study was performed because sufficient information as benzodiazepines and abuse potential is known and the drug is already in Schedule IV CSA. The sponsor proposed placing clobazam in schedule IV, as it is already temporarily listed in the US and internationally scheduled in schedule IV.

diversion.

E. **Integrated abuse potential assessment**

1. ***Findings***

Sponsor identified risks are appropriately identified in label

- Evidence of misuse and diversion in clinical trials

Review of study reports from the Phase 1 and Phase 2/3 studies performed by the sponsor did not show any discontinuations, or protocol deviations or violations related to drug abuse, misuse or diversion.

- Scientific literature-withdrawal reactions

Withdrawal reactions to clobazam are also reported in the scientific literature (Petursson and Lader, 1981)[5] by patients treated with clobazam for anxiety from 6 months to 1 year. Upon discontinuation, the patients developed a withdrawal syndrome typical of the benzodiazepines that included severe insomnia, tension, restlessness, anxiety, panic attacks, hand tremor, profuse sweating, difficulty in concentrating, nausea and dry retching, weight loss, palpitations, blurred vision and photophobia, and muscle pains and stiffness. Their symptoms started soon after discontinuation, and lasted for 8-10 days, followed by rapid improvement.

- Risks of substance and formulation

Concomitant administration of clobazam with alcohol increases maximum exposure of clobazam by 50%. The draft label contains a warning.

Concomitant administration of clobazam with dextromethorphan (and possibly other substances) leads to increases of 90% in AUC and 59% in C_{max} values for dextromethorphan in CYP2D6 extensive metabolizers. See Recommendations.

- Epidemiology data bases related to abuse of product

At the request of CSS, the Office of Surveillance and Epidemiology (OSE) reviewed foreign databases related to misuse, abuse and overdose associated with clobazam. The Division of Pharmacovigilance-I was tasked with assessing cases suggestive of abuse, misuse and

[5] Petursson H, Lader MH. Withdrawal reaction from clobazam. Br Med J (Clin Res Ed). 1981 Jun 13;282(6280):1931-2.

Reference ID: 3016525

overdoses reported in association with clobazam use from the Agency's Adverse Event Reporting System (AERS) database as well as the World Health Organization (WHO) VigiBase database. VigiBase contains individual safety case reports submitted from member countries in the WHO International Drug Monitoring Programme from 1968 until today.

An extensive search of the AERS database revealed only two cases of overdose reported in association with clobazam. The first overdose case occurred in a patient with renal insufficiency who presumably had greater than necessary serum concentrations of several drugs due to his declining renal function. The second overdose case occurred as a consequence of a medication administration error by a healthcare provider. There were no cases of abuse or misuse in AERS.

The WHO VigiBase database provided a handful of cases of drug dependence, overdose, and abuse; but, without narratives, it is not possible to fully assess these cases. Of approximately six million case reports in the database, there were 244 clobazam reports retrieved from the VigiBase database, and 306 unique PTs coded. There were a number of cases identified that were related to drug abuse, misuse and overdose: drug dependence (12), drug abuse (1), withdrawal syndrome (4), drug withdrawal syndrome (1), intentional overdose (6), multiple drug overdoses intentional (2), overdose (1), suicide attempt (5), death (3), and sudden death (1). There were also a number of AEs which could indicate abuse potential of clobazam, such as the following: somnolence (13), aggression (10), depressed level of consciousness (5), sedation (4), confusional state (4), disorientation (4), agitation (3), insomnia (3), personality disorder (3), and mania (1).

OSE concluded that the AERS and WHO data did not demonstrate unequivocal evidence of abuse potential associated with clobazam.

- Postmarketing Foreign experience

The sponsor collected all international postmarketing reports up to July 1, 2010. Periodic Safety Update Reports (PSURs), which were processed and summarized by Aventis Global PV and Epidemiology, were received by Lundbeck Pharmaceuticals. Periodic Safety Update Reports compiled for regulatory authorities by Aventis covered those received from worldwide sources from November 16, 1994 to February 28, 2010. The sponsor states that in the PSURs submitted to the European Medicines Agency by Aventis from Feb 1998 to February 2010, that there were over 3.4 million patient years' of exposure to clobazam. All AE reports from migrated data and reports received by Lundbeck up to July 1 2010, were included in the overall analysis of the PV database in this ISS.

The database consists of 1956 cases reported to the global data base (ISS, table 83, page 178). The most frequent were nervous disorders 1,047 (53.5%), psychiatric 609 (31.1%) and general disorders 567 (29.9%). The sponsor prepared a table of abuse related AEs (ISS, table 107, page 264).[6] ; however, Examination of the original database revealed that the most frequent AEs in the nervous system disorders were: disturbance in consciousness:

[6] An apparently incorrect denominator of 4162 was used instead of 1956. This decreased the percentage ratio of AEs and may have missed other important AEs, including hallucinations, substance-related disorders.

somnolence 214, sedation 18, depressed level of consciousness 22; dizziness 69; memory loss: amnesia 17, and memory impairment 25; psychiatric disorders: agitation 58, anxiety 35, restlessness 9, confusional state 39, disorientation 9, depression 20, hallucinations 25, hallucinations auditory 6, hallucinations visual 6, total 37:, euphoric mood 7, aggression 50, abnormal behavior 21, substance related disorders: drug dependence 16, drug abuse 6, withdrawal syndrome 20, insomnia 53, suicidal ideation 5, suicide attempt 11, and general disorders: fatigue 44, irritability 32, feeling abnormal 16, feeling drunk 6.

Additionally, the sponsor searched Global PV Database for reports from patients taking clobazam for AE terms related to drug overdose or increased drug level.

The search identified 106 unique cases to July 1, 2010. Of these 106 cases, 67 clobazam overdoses were described as 42 multiple drug and/or alcohol overdoses, and 23 reports contained events of increased levels of other AEDs in patients taking clobazam. Two cases did not report sufficient information for further discussion. The remaining 39 cases identified clobazam as the suspect product in accidental or intentional overdose or described patients with increased blood levels of clobazam or N-CLB. Four of 39 cases in this group that included an event term related to clobazam overdose reported a fatal outcome. In the remaining clobazam overdose cases, AEs reported included coma (2 subjects), somnolence or sedation (3 subjects), nausea, asthenia, ataxia, gait disturbance, bradycardia, decreased appetite, fatigue, hyperkinesia, hypotonia, and vertigo.

Generally, as the sponsor states, events were transient and subjects recovered or were recovering at the time of the report. Five cases with a reported event of overdose reported that no AEs occurred.

In the reports where the outcome information was provided, the highest dose of clobazam as a one-time dose was 240 mg; however, the majority of postmarketing cases did not contain dosing information, and dosing in intentional overdose was generally not known.

- Risks associated with accidental use in vulnerable populations identified

The pediatric population of patients with LGS is a vulnerable population because they will constitute the major target for this drug. Accidental exposure and accidental overdose with fatal outcome are possible. The container closure system should be child proof, and the container with the medication should be stored in the place where the child can not reach it. (See Recommendations).

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

/s/

ALICJA LERNER
09/16/2011

MICHAEL KLEIN
09/16/2011

Department Of Health And Human Services

Food And Drug Administration

Center For Drug Evaluation And Research

Office Of Surveillance And Epidemiology

Office Of Medication Error Prevention And Risk Management

Date:	August 29, 2011
Application Type/Number:	NDA 202067
To:	Russell Katz, Director Division of Neurology Products
Through:	Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Lubna Merchant, M.S., Pharm.D, Team Leader Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name and Strengths:	Onfi (Clobazam) Tablets, 5 mg, 10 mg, and 20 mg.
Applicant/sponsor:	Lundbeck Inc.
OSE RCM #:	2011-189

1 INTRODUCTION

This review evaluates the revised labels submitted by the Applicant in response to the labeling recommendations DMEPA provided in OSE review # 2011-189 on May 26, 2011.

2 MATERIAL REVIEWED

DMEPA reviewed the revised labels and labeling submitted by the Applicant on July 15, 2011. See Appendices A and B for labels and labeling. We also evaluated our recommendations made in OSE review #2011-189

3 DISCUSSION

(b) (4)

4 CONCLUSIONS AND RECOMMENDATIONS

The revised labels address DMEPA's previous recommendations except for one issue, (b) (4) . We provide recommendations in Section 4.1 Comments to the Applicant for the container labels. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Laurie Kelley at 301-796-5068.

4.1 COMMENTS TO THE APPLICANT:

A. Proposed container labels and carton labeling (All sizes and strengths):

(b) (4)

Reference ID: 3007560

(b) (4)

(b) (4)

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

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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.

/s/

LUBNA A MERCHANT
08/29/2011

CAROL A HOLQUIST
08/29/2011

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 202067

Name of Drug: Onfi (clobazam) tablet (5mg, 10mg, and 20mg)

Applicant: Lundbeck, Inc.

Labeling Reviewed

Submission Date: December 23, 2010

Receipt Date: December 23, 2010

Background and Summary Description

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 an "X" in the checkbox next to the labeling requirement.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant via electronic correspondence on June 16, 2011. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by July 7, 2011. The resubmitted labeling will be used for further labeling discussions.

See attached RPM labeling review comments for specific details.

Su-Lin Sun 6/21/2011

Regulatory Project Manager Date

Reference ID: 2998581

Chief, Project Management Staff Date

Reference ID: 2998581

NDA 202067 Onfi (clobazam) initial RPM labeling review (original proposed label submitted on 12/23/2010)

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

SU-LIN SUN
08/11/2011

ROBBIN M NIGHSWANDER
08/19/2011

Note: As discussed with Dr Sun, the need for an established pharmacological class will be a matter of review.

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	202067
Generic Name	Onfi (clobazam)
Sponsor	Lundbeck Inc.
Indication	Lennox-Gastaut Syndrome
Dosage Form	Oral Tablets
Drug Class	Benzodiazepine (?)
Therapeutic Dosing Regimen	20 mg and 40 mg b.i.d.; 20 mg up to (b) (4)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not established
Submission Number and Date	SDN 001, 23-Dec-2010
Review Division	DNP
NDA	202067

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of clobazam (40 mg and 160 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference post-dose between clobazam (40 mg and 160 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. After administration of moxifloxacin, the largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was 7.1 ms after Bonferroni adjustment for 4 time points, and the moxifloxacin profile over time is adequately demonstrated in Figure 6.

In this randomized, evaluator blinded, four-treatment-arm parallel study, 280 healthy subjects received clobazam 800 mg, clobazam 1200 mg, placebo, and moxifloxacin 400 mg. The overall summary of findings is presented in Table 1.

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Table 1: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Clobazam (40 mg and 160 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Hour	ΔΔQTcF (ms)	90% CI (ms)
Clobazam 40 mg	3	-2.3	(-5.3, 0.8)
Clobazam 160 mg	6	-4.0	(-6.8, -1.2)
Moxifloxacin 400 mg*	4	11.2	(8.2, 14.2)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.1 ms

The supratherapeutic dose (160 mg) produces mean clobazam C_{max} values 2.7-fold and N-desmethylclozabam C_{max} values 3.9-fold the mean C_{max} for the 40-mg dose, the therapeutic dose. The highest clinical exposure scenario is administration of clobazam with alcohol which increases C_{max} 50%. The largest drug interactions have been with ketoconazole (50% increase in AUC) and omeprazole (40% increase in AUC, 15% increase in C_{max}). The exposures observed in this study following the 160-mg dose cover these scenarios.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

The sponsor proposed the following language in the package insert.

"12.2 Pharmacodynamics
Effects on Electrocardiogram

(b) (4)

2.2 QT-IRT PROPOSED LABEL

We have the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.

12.2 Pharmacodynamics
The effect of clobazam 20 mg and 80 mg administered twice daily on QTc interval was evaluated in a randomized, evaluator blinded, placebo-, and active-controlled (moxifloxacin 400 mg) parallel thorough QT study in 280 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 80 mg twice daily is adequate to represent the high exposure clinical scenario.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Clobazam is a 1, 5 benzodiazepine with anticonvulsant properties. Benzodiazepines are believed to exert most of their effects by interacting with a high affinity GABA receptor thus enhancing GABAA receptor current and therefore increasing GABA-mediated inhibitory effects, with secondary actions at lower affinity sites.

3.2 MARKET APPROVAL STATUS

Clobazam is approved for marketing in the US.

Clobazam was first approved in Australia on 06 February 1970. As of April 2010, clobazam was approved in over 80 countries worldwide. Lundbeck owns clobazam marketing rights for North America, and (b) (4)

3.3 PRECLINICAL INFORMATION

From eCTD 2.4.2.2.3

"Clobazam and its major metabolite N-CLB were evaluated in ICH- and GLP-compliant cardiovascular safety pharmacology studies. In these studies, effects of clobazam and N-CLB were assessed in vitro for inhibition of IKr in HEK293 cells and modulation of electrophysiologic properties of isolated rabbit Purkinje fibers. In addition, the effects of clobazam on blood pressure, heart rate and cardiac electrophysiology were evaluated in conscious dogs given single oral doses.

"Clobazam displayed a concentration dependent inhibition of IKr ranging from 18% to 52% over a 100-fold concentration range (2.5 μM to 250 μM). While N-CLB inhibited hERG currents by up to 48% when tested at concentrations ranging from 1 to 125 μM. Based on the hERG assay alone, the inhibitory effects of clobazam and N-CLB on I Kr suggest that if either compound alone or the two compounds in combination achieve free plasma concentrations in the range of 1 to 2.5 μM (≥300 ng/mL), prolongation of the QT interval might be evident. However, both clobazam and N-CLB caused a concentration dependent decrease in the action potential duration in isolated rabbit Purkinje fibers. Given the hERG results, these findings were unanticipated, as it would be expected that concentrations associated with IKr inhibition would be associated with prolongation of the APD, at least in the case of a selective hERG channel antagonist. The finding of APD shortening is most consistent with inhibition of other, non IKr cardiac ion channels leading to a likely overall lack of significant effect on QT prolongation.

"In the ICH- and GLP-compliant conscious cardiovascular dog safety pharmacology study (Summary 2.6.3 Table 2, ONVC-9034), a decrease in blood pressure, consistent with that reported in anesthetized dogs in the general pharmacology studies, was observed at the highest dose tested (50 mg/kg), which also induced tremors and convulsions. No effects on blood pressure were seen at 1 or 10 mg/kg. In contrast to the studies in anesthetized animals, heart rate was mildly elevated after all doses of clobazam. These findings most likely represent a reflex increase in heart rate in response to mild decreases in blood pressure associated with clobazam administration. However,

changes in blood pressure and heart rate were not considered adverse as they remained within or near historical control ranges. Clobazam was not associated with changes in the QT and QTc intervals. Similar results on cardiac parameters were also seen in non ICH compliant general pharmacology studies.

"Based on the results of the rabbit Purkinje fiber study, both clobazam and N-CLB were associated with minor shortening of the APD60 and APD90 consistent with activity at cardiac ion channels other than hERG. This may explain why changes in QT and QTc were not evident in the telemetered dog study as the activity of these compounds at other ion channels may have mitigated their activity on IKr, with no observable effect on cardiac conduction."

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4

"Overall, 12 (10.1%) clobazam subjects and 37 (31.9%) active control subjects reported treatment-emergent SAEs in Legacy Epilepsy Study 301. The most common (≥ 5.0% of subjects in either treatment group) treatment-emergent SAEs were convulsion in the clobazam group and somnolence in the active control group.

"Additional treatment-emergent SAEs reported by ≥ 2 subjects were self-injurious ideation (2 subjects; 1.7%) in the clobazam group and vomiting, irritability, ataxia, convulsion, and rash (5 subjects each; 4.3%), disturbance in attention, psychomotor hyperactivity, and abnormal behaviour (4 subjects each; 3.4%), aggression and gingival hypertrophy (3 subjects each; 2.6%), and flushing (2 subjects; 1.7%) in the active control group.

"Treatment-emergent treatment-related SAEs reported by ≥ 2 subjects were somnolence (6 subjects; 5.2%), ataxia and irritability (5 subjects each; 4.3%), convulsion, abnormal behaviour, psychomotor hyperactivity, disturbance in attention, vomiting, and rash (4 subjects each; 3.4%), and aggression and gingival hypertrophy (3 subjects each; 2.6%) in the active control group and convulsion (3 subjects; 2.5%) in the clobazam group (ISS Table 6.3.2). No other specific treatment-emergent treatment-related SAE was reported by more than one subject.

"A total of 8 subjects died across the entire clobazam clinical program (Phase 1 studies, Phase 2/3 LGS studies, Legacy Epilepsy Study 301, and Legacy Psychiatry Studies) as of 01 July 2010. Of these 8 subjects, 6 died in Study OV-1004 while receiving clobazam, one died in Legacy Epilepsy Study 301 while receiving carbamazepine, and one died in Legacy Psychiatry Study 410 while receiving placebo. Three of the 6 clobazam subjects died due to events of pneumonia, 2 of which were specifically associated with aspiration. The remaining 3 subjects died at home and the deaths were attributed to their underlying condition of epilepsy. No trends were apparent among the subjects who died with respect to demographic characteristics or clobazam dosing. None of the events that led to death was considered related to clobazam.

"Electrocardiograms were collected in Study OV-1012 in triplicate and were performed at time points on Day -28 and Day -1 (a total of 4 time points), which served as baseline; ECGs were also collected during maintenance at Week 5 (3 time points) and one time point on each of the Week 7 and Week 15 visits. The ECGs were analyzed using

validated digital techniques at a core ECG laboratory. This provided for a robust ECG interval set of determinations at each of the time points used in the study. The full ECG analysis for this study is provided in the Cardiac Safety Report for Study OV-1012.

"The ECG results demonstrated no abnormality in heart rate, atrio-ventricular conduction, as judged by the PR interval duration, or cardiac depolarization, as determined by the QRS interval duration. The evaluation of cardiac repolarization using the Fridericia correction for the QT interval duration showed no signal of any effect nor did the specific outlier analyses.

"No new morphological changes were noted that represented a clear signal of an effect from clobazam. This trial demonstrated no clear signal of any cardiac safety concern with the use of low dose or high dose clobazam. No subject had an SAE or AE leading to study drug discontinuation associated with abnormal ECG findings."

Reviewer's comments: There were no sudden cardiac deaths or ventricular arrhythmias reported in clobazam's clinical program. No clinically relevant ECG changes were reported.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of clobazam's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 70125. The sponsor submitted the study report CV-1022 for clobazam, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A double-blind, double-dummy, randomized, parallel trial in healthy subjects assessing the ECG effects of clobazam following a therapeutic and supratherapeutic dose compared to placebo with moxifloxacin as the active control.

4.2.2 Protocol Number

OV-1022

4.2.3 Study Dates

08 June 2009 - 24 October 2009

4.2.4 Objectives

Primary Objective:

- The primary objective was to evaluate the effect of clobazam and N-desmethylclobazam (N-CLB) on the QT interval with Fridericia correction method (QTcF) following multiple oral doses in healthy adult subjects.

Secondary Objectives:

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- evaluate the effect of clobazam and N-CLB on the corrected QT interval using the Individual correction method (QTcI) and the Bazett correction method (QTcB) in healthy adult subjects.
- evaluate the clobazam dose concentration effect on the ability to delay cardiac repolarization (QT interval).
- characterize the pharmacokinetic profile of clobazam and N-CLB in healthy adult subjects.
- evaluate the safety and tolerability of multiple doses of clobazam in healthy adult subjects.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, double-blinded, double-dummy, placebo-controlled and positive-controlled parallel design with four treatment arms.

Figure 1: OV-1022 Trial Design

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Check-in	Base-line ECG	Treatment Period (a) Days 1-29										PK/ ECG	Study Exit
Day -2	Day -1		1-4	5-8	9-12	13-16	17-19	20-22	23-25	26-28	29 (b)	Days 30-38	Day 39 (c)
		A	Clobazam placebo		20 mg	40 mg					40 mg + MOXI placebo		
		B	20 mg	40 mg	60 mg	80 mg	100 mg	120 mg	140 mg	160 mg	160 mg + MOXI placebo		
		C	Clobazam placebo								CLO placebo + MOXI placebo		
		D	Clobazam placebo								MOXI 400 mg + CLO placebo		
	< ---------- Confinement ---------- >												

Source: Sponsor's ov-1022-synopsis.pdf page 2.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

- Group A: Clobazam 20 mg b.i.d.
- Group B: Clobazam 80 mg b.i.d.
- Group C: Placebo
- Group D: Moxifloxacin 400-mg single dose

Reviewer's comments: Clobazam doses were up-titrated in the trial (see Figure 1).

Reference ID: 2997000

4.2.6.2 Sponsor's Justification for Doses

"The potential therapeutic dose for clobazam is 40 mg, and the doses chosen for this study (40 and 160 mg) represent potential therapeutic and supratherapeutic exposures. The 160 mg supratherapeutic dose was chosen based on safety data from clinical studies in LGS patients, published studies in epilepsy and anxiety, and the recently completed Phase 1 dose ranging study (OV-1038) which determined that the 160 mg was adequately tolerated in healthy volunteers and would be appropriate for use as a supratherapeutic dose in this trial."
Source: Clinical Study Report P-36

Reviewer's Comment: The 160-mg dose is the highest dose tested in humans. The supratherapeutic dose produces clobazam C_{max} values 2.7-fold and N-desmethylclozabam C_{max} values 3.9-fold the mean C_{max} for the intended clinical dose. The highest clinical exposure scenario is administration of clobazam with alcohol which increases C_{max} 50%. The largest drug interactions have been with ketoconazole (50% increase in AUC) and omeprazole (40% increase in AUC, 15% increase in C_{max}). The exposures observed in this study following the 160-mg dose cover these scenarios.

4.2.6.3 Instructions with Regard to Meals

Each morning dose was administered following an overnight fast (at least 10 hours) with approximately 240 mL of water. Subjects abstained from water consumption from 1 hour prior to all doses through 2 hours after the morning dose and 1 hour after the evening dose. Food was allowed 2 hours after the morning dose and1 hour after the evening dose.

Reviewer's Comment: Administration under fasting conditions is acceptable. Food did not have a significant effect on clobazam or N-desmethylclobazam exposure.

4.2.6.4 ECG and PK Assessments

ECGs from the Holter recordings were extracted on Days -1 and 29 pre-dose (-0.25 hours), and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 23.5 hours post-dose.

Blood samples for pharmacokinetic analysis of clobazam and N-desmethylclobazam were collected pre-dose on Days 1, 26, 27 and 28. On Day 29 samples were collected pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, 12, 16 and 24 hours post-dose.

Reviewer's Comment: The timing of the PK and ECGs is adequate to capture the QT effect at peak concentrations of clobazam (T_{max} ~ 3.5 hours) and N-desmethylclobazam (T_{max} ~ 2.2 hours,) and potential delayed effect up to 24 hours post-dose.

4.2.6.5 Baseline

The sponsor used time-matched QTc values collected on Day -1 as baseline values.

4.2.7 ECG Collection

On Days -1 and 29, digital electrocardiogram (ECG) readings from Holter monitors were extracted serially over the 23.5-hour postdose interval relative to dosing on Day 29, and at identical timepoints on Day -1 (Baseline).
At each timepoint, an ECG was extracted in triplicate within a 6-minute window beginning at the nominal ECG timepoint. Select timepoints were read with a manual

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over-read at a central ECG laboratory. All continuous 12-lead ECGs were read by a blinded cardiologist for interval measurements and overall interpretation.

Subjects refrained from talking and remained in a supine position from approximately 10 minutes prior to until 6 minutes following the nominal timepoints. Pharmacokinetic blood sample collections at the corresponding nominal timepoints were to occur immediately following (within 5 minutes) the ECG extraction window.

All Holter monitor data were downloaded or shipped to the CRO prior to unblinding. ECGs were sent to a central laboratory, (b) (4) for high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment.

In addition, standard 12-lead ECGs for safety monitoring were performed at Screening, Check-in (Day -2), at 0 (predose), 1, 4, and 8 hours following the morning dose on Days 1, 5, 9, 13, 17, 20, 23 and 26, and prior to discharge at Study Exit/Early Withdrawal.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 280 subjects were enrolled and 258 subjects (92%) completed the study. Among the 22 subjects who prematurely discontinued, 6 were in the clobazam 40-mg TDD group, 9 were in the clobazam 160-mg TDD group, 3 were in the placebo group, and 4 were in the moxifloxacin 400-mg group.

Table 2: Subject Demographics and Baseline Characteristics (Safety Population)

	Clobazam 40 mg TDD N = 70	Clobazam 160 mg TDD N = 70	Placebo N = 70	Moxifloxacin 400 mg TDD N = 70	Total N = 280
Gender (n, %)					
Men	35 (50.0%)	38 (54.3%)	40 (57.1%)	34 (48.6%)	147 (52.5%)
Women	35 (50.0%)	32 (45.7%)	30 (42.9%)	36 (51.4%)	133 (47.5%)
Race (n, %)					
White	52 (74.3%)	57 (81.4%)	57 (81.4%)	58 (82.9%)	224 (80.0%)
Black/African American	18 (25.7%)	12 (17.1%)	13 (18.6%)	12 (17.1%)	55 (19.6%)
Other	0	1 (1.4%)	0	0	1 (0.4%)
Ethnicity (n, %)					
Hispanic/Latino	62 (88.6%)	65 (92.9%)	62 (88.6%)	65 (92.9%)	254 (90.7%)
Not Hispanic/Latino	8 (11.4%)	5 (7.1%)	8 (11.4%)	5 (7.1%)	26 (9.3%)
Age (yr)					
Mean (SD)	34.5 (7.01)	34.1(6.64)	33.6 (7.66)	34.4 (6.72)	34.2 (6.99)
Range	19.8 – 45.8	18.6 – 45.7	18.1 – 45.8	20.2 – 45.8	18.1 – 45.8
Height (cm)					
Mean (SD)	168.4 (9.01)	168.1 (8.59)	168.4 (8.51)	167.5 (8.48)	168.1 (8.61)
Range	155.0 – 189.5	152.0 – 190.0	150.0 – 188.0	144.0 – 187.0	144.0 – 190.0
Weight (kg)					
Mean (SD)	72.6 (11.40)	73.9 (10.21)	72.5 (11.24)	72.2 (11.38)	72.8 (11.03)
Range	54.0 – 96.1	50.6 – 105.0	50.0 – 102.0	50.4 – 100.3	50.0 – 105.0
Body mass index (kg/m^2)					
Mean (SD)	25.5 (2.80)	26.1 (2.43)	25.5 (2.72)	25.6 (2.58)	25.7 (2.63)
Range	19.1– 29.8	19.6 – 29.5	19.7 – 29.9	19.9 – 29.7	19.1 – 29.9

Source: End-of-Text Table 14.1.2.1.

Source: CSR, Table 12

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the change from the baseline-adjusted mean difference between clobazam 40 mg and placebo, and clobazam 160 mg and placebo in QTcF. The sponsor used a mixed effects model with treatment, gender, time, and time-by-treatment interaction as fixed effects and subject as a random effect. Sponsor's results are in Table 3. The sponsor found that the 40-mg and 160-mg dosages of clobazam did not result in elongated QT intervals.

Table 3: Sponsor's Result of ΔΔQTcF for Clobazam 40 mg and 160 mg

(Largest Mean Difference from Baseline, with 90% Confidence Bounds)

Hour	ΔΔQTcF: moxifloxacin		Hour	ΔΔQTcF: clobazam 40 mg		Hour	ΔΔQTcF: clobazam 160 mg	
	Mean	90% CI		Mean	90% CI		Mean	90% CI
4	11.6	(8.5, 14.8)	3	-2.0	(-4.2, 0.1)	6	-3.2	(-5.4, -1.0)

Reviewer's Comments: Our independent analysis agrees with the sponsor's results. Our results are reported in Section 5.2.

4.2.8.2.2 Assay Sensitivity

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The minimum lower limit of the 90% CIs for ΔΔQTcF moxifloxacin was above 5 ms, demonstrating assay sensitivity. Our independent analysis agrees with the final conclusions reported by the sponsor (see 5.2).

4.2.8.2.3 Categorical Analysis

Our independent categorical analysis agrees with the categorical analysis reported by the sponsor (see 5.2).

4.2.8.3 Safety Analysis

Thirteen subjects were discontinued due to adverse events. Three subjects (1005, 1050, and 1247) were in the clobazam 40-mg TDD group, 7 subjects (1004, 1008, 1021, 1090, 1132, 1136, and 1191) were in the clobazam 160-mg TDD group, 2 subjects (1022 and 1144) were in the placebo group, and 1 subject (1255) was from the moxifloxacin group. The primary reasons for discontinuation were elevations in liver enzymes in the clobazam 40-mg TDD and moxifloxacin groups, drowsiness/delirium in the clobazam 160 -mg TDD group, and sinus tachycardia in the placebo group.

A total of 8 subjects withdrew consent. Three of these subjects (1058, 1212, and 1267) were in the clobazam 40-mg TDD group, one subject (1076) was in the clobazam 160-mg TDD group, 1 subject (1239) was in the placebo group, and 3 subjects (1010, 1053, and 1105) were in the moxifloxacin group. In addition, Subject 1153 in the clobazam 160-mg TDD group was withdrawn after regurgitating partially dissolved pill material.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 4 for clobazam and N-desmethylclobazam, and Table 5 for moxifloxacin. C_{max} and AUC values of clobazam in the thorough QT study were 2.5 to 2.7-fold higher following administration of 160 mg clobazam compared with 40 mg clobazam. C_{max} and AUC values of N-desmethylclobazam in the thorough QT study were 3.9-fold higher following administration of 160 mg clobazam compared with 40 mg clobazam. Time courses of clobazam and N-desmethylclobazam are illustrated in Figure 2.

Table 4: Mean (%CV) Pharmacokinetic Parameters of Clobazam and N-Desmethylclobazam on Day 29

	Clobazam 40 mg TDD Day 29 N = 66				Clobazam 160 mg TDD Day 29 N = 62			
	Pharmacokinetic Population		Excluding Poor Metabolizers (a)		Pharmacokinetic Population		Excluding Poor Metabolizers (a)	
Clobazam	**n**	**Mean(%CV)**	**n**	**Mean(%CV)**	**n**	**Mean(%CV)**	**n**	**Mean(%CV)**
$AUC_{0\text{-}tau}$ (ng•hr/mL)	66	10,350 (26%)	64	10,394 (26%)	62	25,445 (18%)	60	25,658 (18%)
$AUC_{0\text{-}24}$ (ng•hr/mL)	66	17,649 (28%)	64	17,744 (29%)	62	41,389 (20%)	60	41,831 (19%)
C_{max} (ng/mL)	66	1,076 (24%)	64	1,081 (24%)	62	2,884 (18%)	60	2,902 (17%)
t_{max} (hr) (b)	66	1.62 (0.62 – 6.12)	64	1.62 (0.62 – 6.12)	62	1.87 (0.62 – 6.12)	60	2.12 (0.62 – 6.12)
C_{min} (ng/mL) (c)	66	708 (31%)	64	713 (31%)	62	1,641 (22%)	60	1,660 (21%)
C_{ave} (ng/mL)	66	863 (26%)	64	866 (26%)	62	2,120 (18%)	60	2,138 (18%)
CL/F (L/hr)	66	2.06 (26%)	64	2.06 (26%)	62	3.26 (20%)	60	3.23 (19%)
CL/F/70 kg (L/hr/kg)	66	2.03 (31%)	64	2.03 (32%)	62	3.18 (26%)	60	3.15 (26%)
V_{ss}/F (L)	58	113 (27%)	56	114 (27%)	62	128 (26%)	60	129 (25%)
V_{ss}/F/70/kg (L/kg)	58	111 (27%)	56	111 (27%)	62	123 (25%)	60	124 (25%)
Fluctuation	66	0.45 (39%)	64	0.45 (39%)	62	0.60 (33%)	60	0.59 (33%)
N-CLB								
$AUC_{0\text{-}tau}$ (ng•hr/mL)	66	30,464 (66%)	64	28,285 (55%)	62	117,405 (55%)	60	108,809 (41%)
$AUC_{0\text{-}24}$ (ng•hr/mL)	66	57,693 (65%)	64	53,620 (55%)	62	223,023 (55%)	60	206,768 (41%)
C_{max} (ng/mL)	66	2,783 (71%)	64	2,563 (57%)	62	11,020 (60%)	60	10,084 (41%)
t_{max} (hr) (b)	66	4.12 (0.00 – 12.12)	64	4.12 (0.00 – 12.12)	62	4.12 (0.00 – 12.12)	60	4.12 (0.00 – 12.12)
C_{min} (ng/mL) (c)	66	2,433 (65%)	64	2,275 (58%)	62	9,576 (64%)	60	8,698 (43%)
C_{ave} (ng/mL)	66	2,539 (66%)	64	2,357 (55%)	62	9,784 (55%)	60	9,067 (41%)
Fluctuation	66	0.14 (96%)	64	0.13 (96%)	62	0.16 (77%)	60	0.16 (76%)

(a) CYP2C19 poor metabolizers excluded (Subjects 1040 and 1250 in the 40 mg TDD group, and Subjects 1025 and 1088 in the 160 mg TDD group).
(b) Median (range) for t_{max}. t_{max} was reported as actual times. Most actual sample times were 7 minutes later than scheduled due to the site performing the ECG first at the scheduled time point.
(c) Predose concentration on Day 29.
NOTE: No summary statistics were reported for $t_{1/2}$, λ_z, or MRT for N-CLB due to a lack of a clear terminal phase in the majority of the pharmacokinetic profiles.

Source: Clinical Study Report P-61, Table 14.

Table 5: Mean (%CV) Pharmacokinetic Parameters of Moxifloxacin on Day 29

	Mean (%CV) N = 66
Moxifloxacin	
$AUC_{0\text{-}lqc}$ (ng•hr/mL)	33,545 (19%)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	34,482 (18%)
C_{max} (ng/mL)	2,370 (27%)
t_{max} (hr) (a)	2.62 (1.12 – 6.12)
$t_{1/2}$ (hr)	13.3 (18%)

(a) Median (range) for t_{max}.

Source: Clinical Study Report P-63, Table 16.

Reference ID: 2997000

Figure 2: Mean Plasma Concentrations of Clobazam and N-desmethylclobazam (N-CLB) on Day 29

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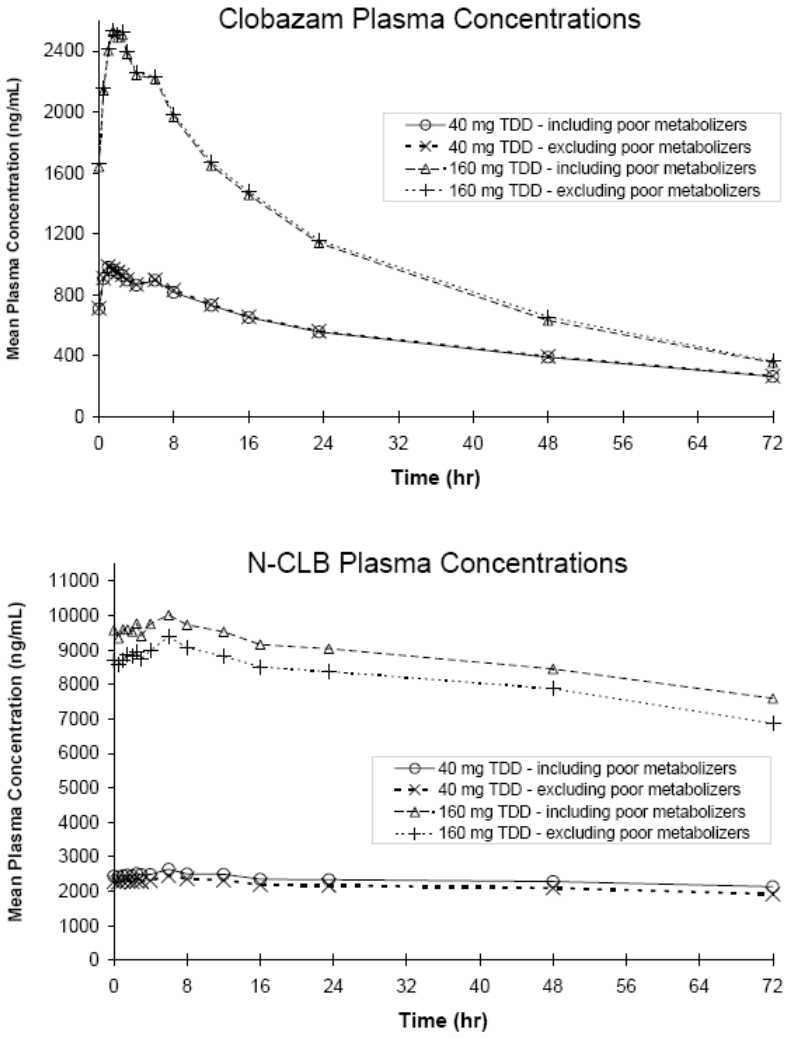

Source: Clinical Study Report P-59, Figure 2.

4.2.8.4.2 Exposure-Response Analysis

The relationship between placebo corrected changes from baseline in QTcF and clobazam and N-desmethylclobazam plasma concentrations are provided in Figure 3 and Figure 4, respectively. In the linear mixed-effects model for the relationship between change from baseline QTcF and C_{max} plasma concentration of clobazam and N-desmethylclobazam, the predicted placebo-corrected change from baseline of QTcF at the mean maximum concentrations of clobazam and N-desmethylclobazam were less than -2.20 ms with the upper limit of the corresponding 90% CIs less than 0 ms.

Figure 3: QTcF Placebo-Corrected Change from Baseline versus Clobazam Plasma Concentration

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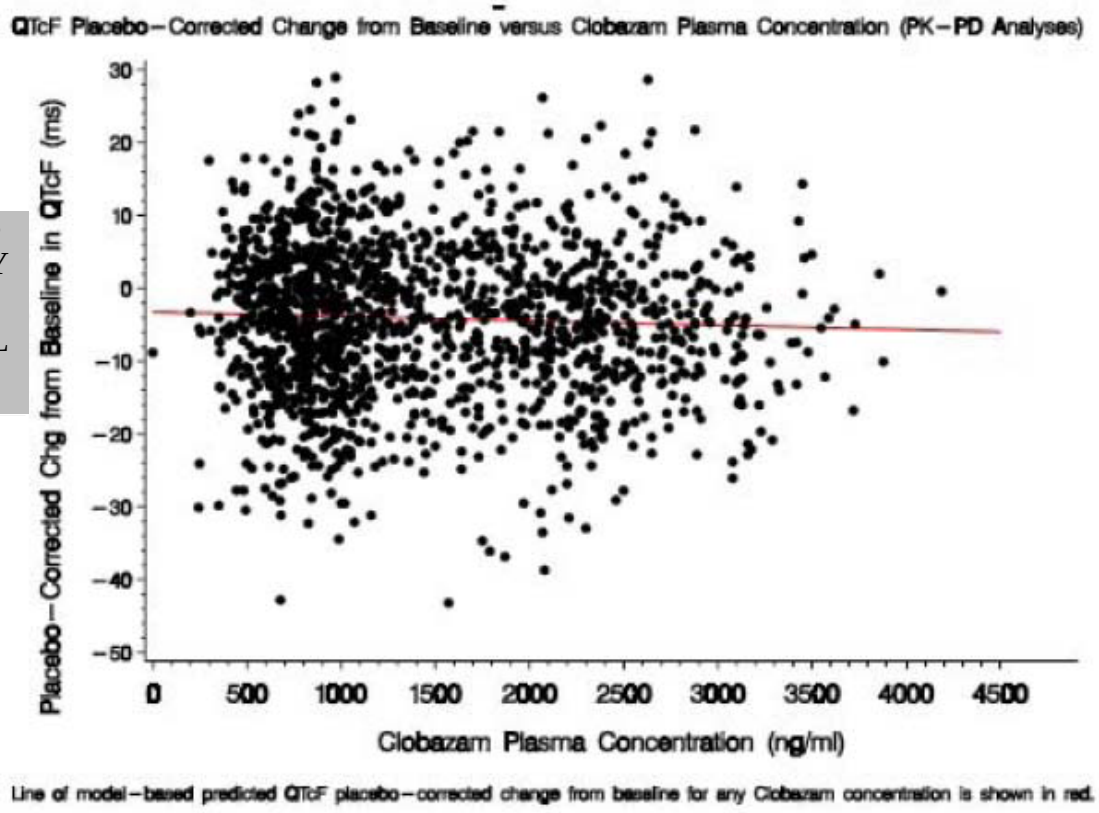

Source: Clinical Study Report P-75, Figure 4.

Figure 4: QTcF Placebo-Corrected Change from Baseline versus N-Desmethylclobazam (N-CLB) Plasma Concentration

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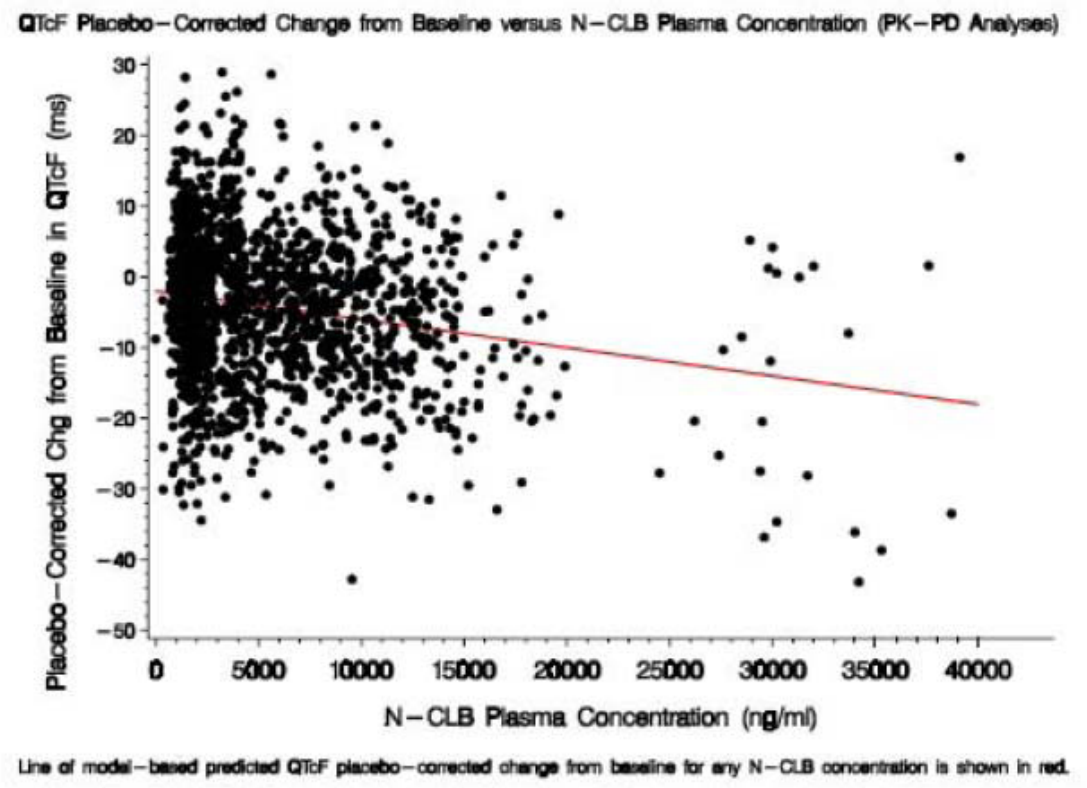


Source: Clinical Study Report P-76, Figure 5.

Reviewer's Analysis: Our independent plots of ΔΔQTcF vs. clobazam and N-desmethylclobazam concentrations are presented in Figure 7 and Figure 8, respectively.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 6, it appears that QTcF had smaller absolute slopes than QTcI. Therefore, QTcF is a better correction method for the study data.

Table 6: Comparison of QTcF and QTcI Using the Mixed Model

Treatment Groups	Slope of QTcF	Slope of QTcI	P_value
Clobazam 160 mg	0.0085	0.0113	0.3896
Clobazam 40 mg	0.0117	0.0259	0.0000
Moxifloxacin 400 mg	0.0103	0.0247	0.0000
Placebo	0.0093	0.0143	0.0950
All	0.0097	0.0196	0.0000

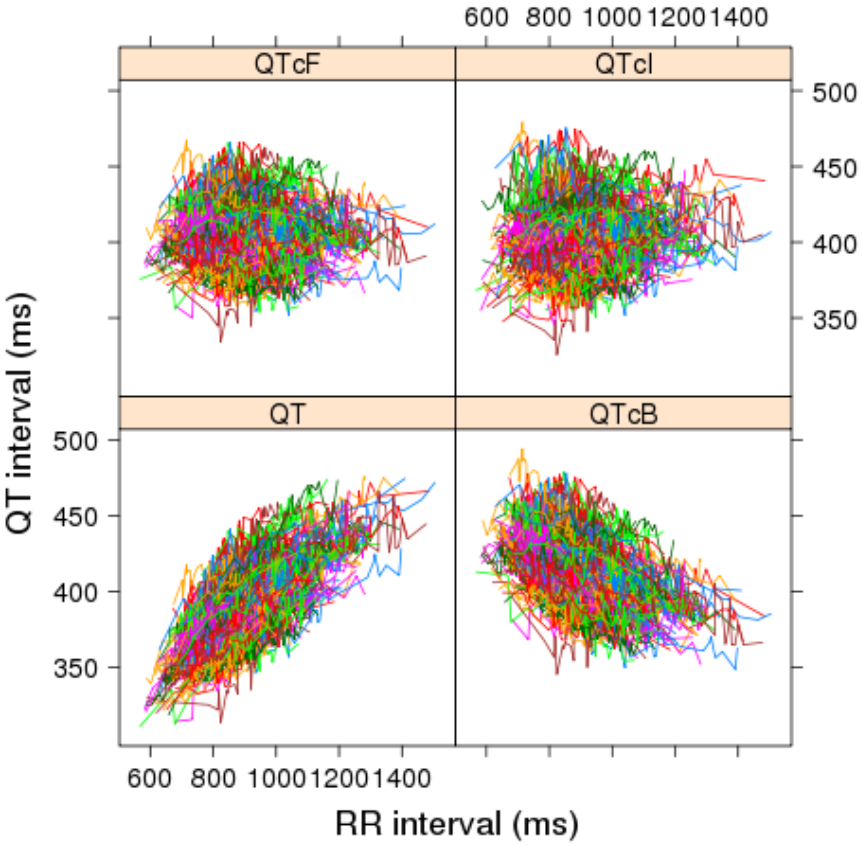
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 7, it also appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 7: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	QTcF		QTcI	
Treatment Group	**N**	**MSSS**	**N**	**MSSS**
Clobazam 160 mg	68	0.0024	68	0.0026
Clobazam 40 mg	69	0.0031	69	0.0037
Moxifloxacin 400 mg	69	0.0026	69	0.0038
Placebo	69	0.0030	69	0.0033
All	275	0.0028	275	0.0034

The relationship between different correction methods and RR is presented in Figure 5.

Figure 5: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



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5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Clobazam

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment as a fixed effect and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Reference ID: 2997000

Table 8: Analysis Results of ΔQTcF and ΔΔQTcF for Clobazam 40 mg x 20 days

	ΔQTcF: clobazam			ΔQTcF: placebo			ΔΔQTc			
Time/(hr)	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	67	-6.7	1.2	67	-4.3	1.2	67	-2.5	1.7	(-5.3, 0.4)
1	67	-5.6	1.3	67	-1.6	1.3	67	-4.0	1.9	(-7.1, -0.9)
1.5	67	-5.2	1.2	67	-1.5	1.2	67	-3.7	1.7	(-6.6, -0.9)
2	67	-4.5	1.2	67	-0.3	1.2	67	-4.2	1.6	(-6.9, -1.5)
2.5	67	-5.6	1.3	67	-1.1	1.3	67	-4.5	1.8	(-7.4, -1.5)
3	67	-4.4	1.3	67	-2.1	1.3	67	-2.3	1.8	(-5.3, 0.8)
4	67	-4.6	1.3	67	0.8	1.3	67	-5.5	1.8	(-8.5, -2.5)
6	67	-0.4	1.2	67	2.1	1.2	67	-2.5	1.7	(-5.3, 0.3)
8	69	-3.3	1.2	67	1.6	1.2	67	-4.8	1.6	(-7.6, -2.1)
12	67	-3.8	1.1	68	-1.1	1.1	67	-2.7	1.5	(-5.3, -0.2)
16	67	-3.2	1.2	69	-0.6	1.2	67	-2.6	1.7	(-5.5, 0.2)
23.5	68	-1.8	1.2	69	1.2	1.1	68	-3.0	1.6	(-5.6, -0.3)

Table 9: Analysis Results of ΔQTcF and ΔΔQTcF for Clobazam 160 mg x 20 days

	ΔQTcF: clobazam			ΔQTcF: placebo			ΔΔQTc			
Time/(hr)	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	63	-9.3	1.2	67	-4.3	1.2	63	-5.1	1.7	(-7.9, -2.2)
1	61	-8.0	1.4	67	-1.6	1.3	61	-6.5	1.9	(-9.7, -3.3)
1.5	62	-7.2	1.3	67	-1.5	1.2	62	-5.7	1.8	(-8.6, -2.8)
2	62	-6.6	1.2	67	-0.3	1.2	62	-6.3	1.7	(-9.1, -3.5)
2.5	62	-7.2	1.3	67	-1.1	1.3	62	-6.0	1.8	(-9.1, -3.0)
3	64	-7.0	1.3	67	-2.1	1.3	64	-4.9	1.9	(-8.0, -1.8)
4	65	-6.3	1.3	67	0.8	1.3	65	-7.1	1.8	(-10.1, -4.1)
6	65	-1.9	1.2	67	2.1	1.2	65	-4.0	1.7	(-6.8, -1.2)
8	66	-3.1	1.2	67	1.6	1.2	66	-4.7	1.7	(-7.4, -1.9)
12	65	-5.3	1.1	68	-1.1	1.1	65	-4.2	1.6	(-6.8, -1.6)
16	66	-5.8	1.2	69	-0.6	1.2	66	-5.3	1.7	(-8.1, -2.4)
23.5	67	-5.1	1.2	69	1.2	1.1	67	-6.3	1.6	(-9.0, -3.6)

The largest upper bounds of the 2-sided 90% CI for the mean difference between clobazam 40 mg and placebo, and between clobazam 160 mg and placebo were 0.8 ms and -1.2 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table **10**. The largest unadjusted 90% lower confidence interval is 8.2 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 7.1 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Reference ID: 2997000

Table 10: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

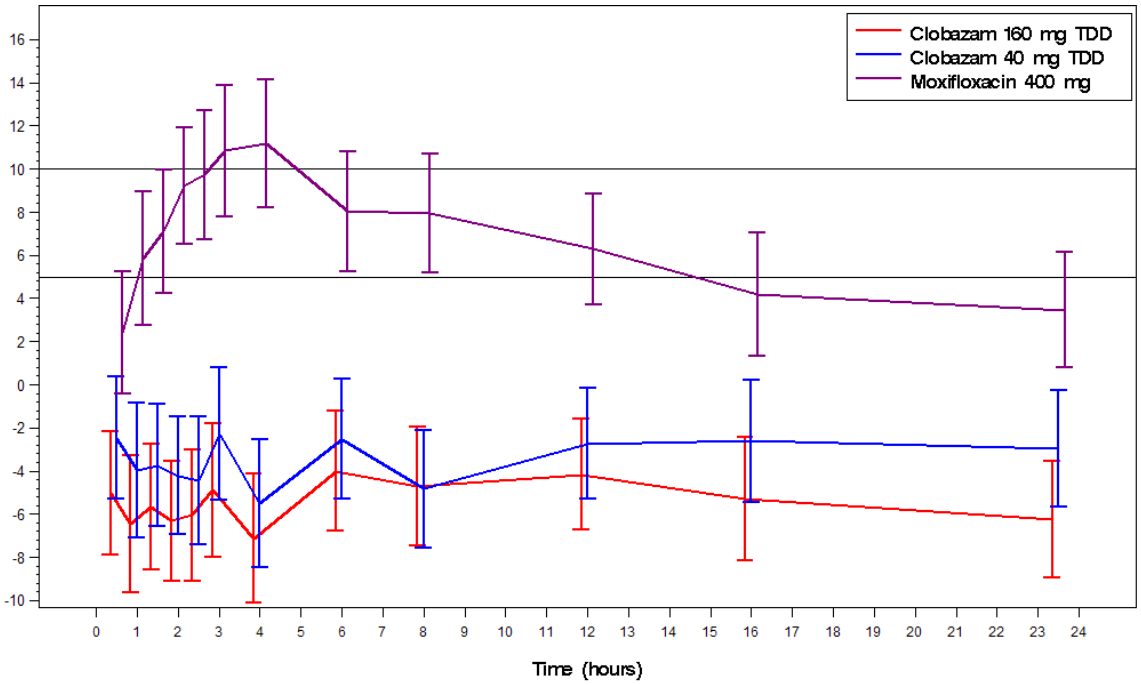
	ΔQTc: moxifloxacin			ΔQTc: placebo			ΔΔQTc				
Time/(hr)	N	Mean	SD	N	Mean	SD	N	Mean	SD	Unadjusted 90% CI	Adjusted* 90% CI
0.5	67	-1.9	1.2	67	-4.3	1.2	67	2.4	1.7	(-0.4, 5.2)	(-1.4, 6.3)
1	67	4.3	1.3	67	-1.6	1.3	67	5.8	1.9	(2.7, 9.0)	(1.6, 10.1)
1.5	67	5.6	1.2	67	-1.5	1.2	67	7.1	1.7	(4.2, 9.9)	(3.2, 11.0)
2	67	9.0	1.2	67	-0.3	1.2	67	9.2	1.6	(6.5, 11.9)	(5.5, 12.9)
2.5	67	8.6	1.3	67	-1.1	1.3	67	9.7	1.8	(6.7, 12.7)	(5.7, 13.8)
3	67	8.7	1.3	67	-2.1	1.3	67	10.8	1.8	(7.8, 13.9)	(6.7, 15.0)
4	67	12.0	1.3	67	0.8	1.3	67	11.2	1.8	(8.2, 14.2)	(7.1, 15.2)
6	67	10.1	1.2	67	2.1	1.2	67	8.0	1.7	(5.3, 10.8)	(4.2, 11.8)
8	67	9.5	1.2	67	1.6	1.2	67	8.0	1.7	(5.2, 10.7)	(4.2, 11.7)
12	66	5.2	1.1	68	-1.1	1.1	66	6.3	1.6	(3.7, 8.8)	(2.8, 9.8)
16	68	3.6	1.2	69	-0.6	1.2	68	4.2	1.7	(1.3, 7.0)	(0.3, 8.1)
23.5	68	4.6	1.2	69	1.2	1.1	68	3.5	1.6	(0.8, 6.2)	(-0.2, 7.1)

* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 6: Mean and 90% CI ΔΔQTcF Timecourse



All CIs are unadjusted, including moxifloxacin.

5.2.1.4 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 11: Categorical Analysis for QTcF

Treatment Group	N	Value<=450 ms	450 ms<Value<=480 ms
Clobazam 160 mg	68	67 (98.5%)	1 (1.5%)
Clobazam 40 mg	69	67 (97.1%)	2 (2.9%)
Moxifloxacin 400 mg	69	66 (95.7%)	3 (4.3%)
Placebo	69	64 (92.8%)	5 (7.2%)

Table 12 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Reference ID: 2997000

Table 12: Categorical Analysis of ΔQTcF

Treatment Group	N	Value<=30 ms	30 ms<Value<=60 ms
Clobazam 160 mg	68	68 (100%)	0 (0.0%)
Clobazam 40 mg	69	69 (100%)	0 (0.0%)
Moxifloxacin 400 mg	69	61 (88.4%)	8 (11.6%)
Placebo	69	69 (100%)	0 (0.0%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 13 and Table 14. The largest upper limits of 90% CI for the PR mean differences between clobazam 40 mg and placebo and clobazam 160 mg and placebo are 7.4 ms and 6.4 ms, respectively.

The outlier analysis results for PR are presented in Table 15.

Table 13: Analysis Results of ΔPR and ΔΔPR for Clobazam 40 mg x 20 days

	ΔPR: Clobazam			ΔPR:Placebo			ΔΔPR			
Time	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	67	5.2	1.1	67	4.2	1.1	67	1.0	1.6	(-1.7, 3.6)
1	67	5.3	1.3	67	3.6	1.3	67	1.7	1.8	(-1.2, 4.7)
1.5	67	4.5	1.2	67	1.7	1.2	67	2.7	1.6	(0.0, 5.4)
2	67	5.6	1.3	67	1.3	1.3	67	4.2	1.9	(1.1, 7.4)
2.5	67	5.1	1.0	67	2.3	1.0	67	2.8	1.5	(0.4, 5.2)
3	67	5.1	1.2	67	0.9	1.2	67	4.2	1.7	(1.4, 6.9)
4	67	5.3	1.1	67	2.1	1.1	67	3.2	1.5	(0.6, 5.7)
6	67	3.2	1.0	67	2.3	1.0	67	0.9	1.4	(-1.5, 3.2)
8	69	2.7	1.1	67	2.9	1.1	67	-0.3	1.5	(-2.8, 2.2)
12	67	3.5	0.9	68	1.4	0.9	67	2.1	1.3	(-0.0, 4.3)
16	67	1.8	1.2	69	0.6	1.2	67	1.3	1.7	(-1.5, 4.0)
23.5	68	3.4	1.1	69	0.0	1.1	68	3.3	1.6	(0.7, 6.0)

Table 14: Analysis Results of ΔPR and ΔΔPR for Clobazam 160 mg x 20 days

	ΔPR: Clobazam			ΔPR:Placebo			ΔΔPR			
Time	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**90% CI**
0.5	63	5.8	1.2	67	4.2	1.1	63	1.6	1.6	(-1.1, 4.3)
1	61	7.0	1.3	67	3.6	1.3	61	3.4	1.8	(0.4, 6.4)
1.5	62	4.4	1.2	67	1.7	1.2	62	2.6	1.7	(-0.1, 5.4)
2	62	4.0	1.4	67	1.3	1.3	62	2.7	1.9	(-0.5, 5.9)
2.5	62	3.5	1.1	67	2.3	1.0	62	1.1	1.5	(-1.4, 3.6)
3	64	4.2	1.2	67	0.9	1.2	64	3.3	1.7	(0.5, 6.1)
4	65	5.3	1.1	67	2.1	1.1	65	3.2	1.6	(0.6, 5.8)
6	65	2.8	1.0	67	2.3	1.0	65	0.4	1.4	(-2.0, 2.8)
8	66	3.6	1.1	67	2.9	1.1	66	0.6	1.5	(-1.9, 3.2)
12	65	3.4	0.9	68	1.4	0.9	64	2.0	1.3	(-0.2, 4.2)
16	66	0.9	1.2	69	0.6	1.2	66	0.3	1.7	(-2.4, 3.1)
23.5	67	3.0	1.1	69	0.0	1.1	67	3.0	1.6	(0.3, 5.6)

Table 15: Categorical Analysis for PR

Treatment Group	**N**	**PR < 200 ms**	**PR >=200 ms**
Clobazam 160 mg	68	60 (88.2%)	8 (11.8%)
Clobazam 40 mg	69	64 (92.8%)	5 (7.2%)
Placebo	69	65 (94.2%)	4 (5.8%)

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16 and Table 17. The largest upper limits of 90% CI for the QRS mean differences between clozabam 40 mg and placebo and clobazam 160 mg and placebo are 1.5 ms and 1.0 ms, respectively.

Reference ID: 2997000

Table 16: Analysis Results of ΔQRS and ΔΔQRS for Clobazam 40 mg x 20 days

	ΔQRS: Clobazam			ΔQRS: Placebo			ΔΔQRS			
Time	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**90% CI**
0.5	67	1.2	0.5	67	1.2	0.5	67	-0.0	0.7	(-1.2, 1.2)
1	67	0.9	0.5	67	0.9	0.5	67	-0.0	0.7	(-1.2, 1.2)
1.5	67	0.7	0.5	67	0.3	0.5	67	0.4	0.7	(-0.8, 1.5)
2	67	0.7	0.5	67	0.4	0.5	67	0.4	0.7	(-0.8, 1.5)
2.5	67	0.6	0.5	67	0.7	0.5	67	-0.1	0.7	(-1.4, 1.1)
3	67	0.4	0.5	67	0.8	0.5	67	-0.4	0.7	(-1.5, 0.8)
4	67	0.8	0.5	67	0.7	0.5	67	0.1	0.7	(-1.1, 1.3)
6	67	0.0	0.5	67	-0.2	0.5	67	0.2	0.8	(-1.1, 1.4)
8	69	0.1	0.5	67	0.2	0.5	67	-0.0	0.7	(-1.2, 1.1)
12	67	-0.2	0.5	68	0.3	0.5	67	-0.5	0.7	(-1.6, 0.6)
16	67	-0.3	0.5	69	0.4	0.5	67	-0.7	0.7	(-1.8, 0.4)
23.5	68	0.4	0.5	69	0.1	0.5	68	0.2	0.7	(-1.0, 1.5)

Table 17: Analysis Results of ΔQRS and ΔΔQRS for Clobazam 160 mg x 20 days

	ΔQRS: Clobazam			ΔQRS: Placebo			ΔΔQRS			
Time	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**90% CI**
0.5	63	0.9	0.5	67	1.2	0.5	63	-0.3	0.7	(-1.5, 0.9)
1	61	0.5	0.5	67	0.9	0.5	61	-0.4	0.7	(-1.6, 0.8)
1.5	62	0.1	0.5	67	0.3	0.5	62	-0.2	0.7	(-1.3, 1.0)
2	62	0.1	0.5	67	0.4	0.5	62	-0.3	0.7	(-1.5, 0.9)
2.5	62	-0.1	0.5	67	0.7	0.5	62	-0.8	0.8	(-2.0, 0.5)
3	64	0.4	0.5	67	0.8	0.5	64	-0.4	0.7	(-1.6, 0.7)
4	65	0.3	0.5	67	0.7	0.5	65	-0.4	0.7	(-1.6, 0.7)
6	65	-0.5	0.5	67	-0.2	0.5	65	-0.4	0.8	(-1.6, 0.9)
8	66	-0.6	0.5	67	0.2	0.5	66	-0.7	0.7	(-1.9, 0.5)
12	65	-0.2	0.5	68	0.3	0.5	65	-0.5	0.7	(-1.6, 0.6)
16	66	-0.8	0.5	69	0.4	0.5	66	-1.2	0.7	(-2.4, -0.1)
23.5	67	-0.3	0.5	69	0.1	0.5	67	-0.5	0.7	(-1.7, 0.7)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationships between ΔΔQTcF and clobazam and N-desmethylclobazam concentrations are visualized in Figure 7 and Figure 8, respectively with no evident concentration-dependent QTc interval increase.

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Figure 7: ΔΔ QTcF vs. Clobazam Concentration

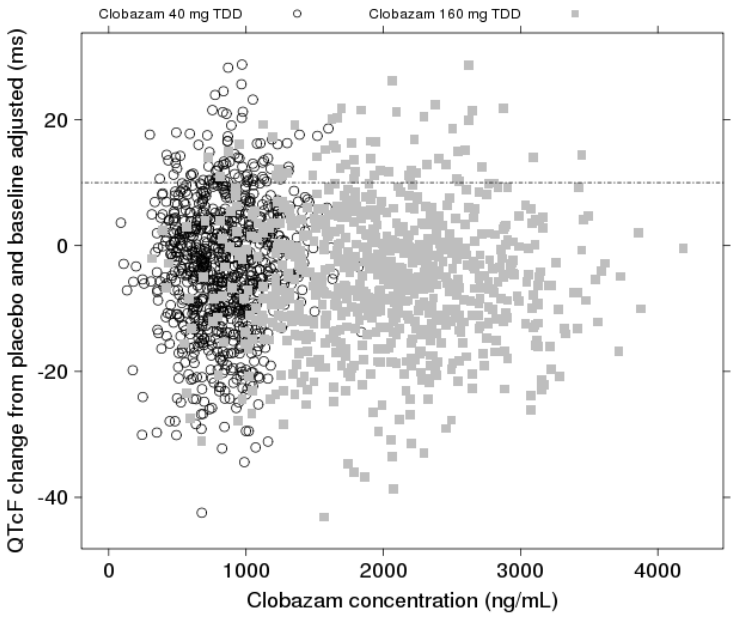
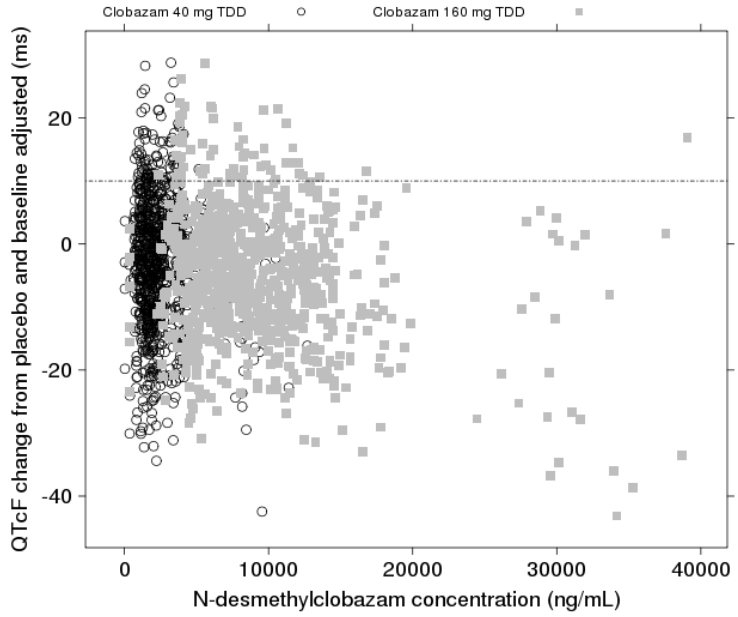


Figure 8: ΔΔ QTcF vs. N-desmethylclobazam Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistic 97% of the ECGs were annotated in the primary lead II, with less than 0.04 % of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Thirteen subjects had a PR>200ms. Two subjects had baseline values >200ms. PR increases were ≤20% of baseline values.

Reference ID: 2997000

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Table 1: Highlights of Clobazam Clinical Pharmacology

Description	Result
Therapeutic Dose	The target maximum daily dose for the Phase 3 clinical study is 1.0 mg/kg or 40 mg. The maximum recommended dose for treatment of LGS is 40 mg/day.
Maximum Tolerated Dose	A MTD is not established in humans. In Phase I trials, up to 160 mg total daily dose (TDD) have been studied.
Principle Adverse Events	In the studies that reported the overall percentage of patients who experienced adverse events (AEs) with clobazam therapy, the numbers varied widely from 0% to 85%, but generally were approximately 40%. The most common AEs reported in this population included sedation, behavioral abnormalities, ataxia, and drooling. Clobazam was generally well tolerated, with most AEs being mild or moderate in severity and transient in nature. Among studies that reported this information, the percentage of patients requiring a reduction in clobazam dosage due to AEs ranged from 0% to 36%, while the number of patients who discontinued clobazam therapy due to AEs ranged from 0% to 31%. AEs that were most often cited as reasons for dosage reduction and/or discontinuation of clobazam included drowsiness, behavioral changes, ataxia, emotional lability, and increased seizure frequency.
Maximum Dose Tested	
Single Dose	160 mg TDD; 80 mg BID titrated for 3 days
Multiple Dose	120 mg TDD; 60 mg BID titrated to steady state
Exposure Achieved at Maximum Tested Dose	
Single Dose	160 mg; Clobazam: Cmax =3091 ng/mL, AUC0-tau = 26092 ng·hr/mL; N-desmethylclobazam: Cmax =7361 ng/mL, AUC0-tau = 84401 ng·hr/mL
Multiple Dose	120 mg; Clobazam: Cmax =2629 ng/mL, AUC0-tau =19867 ng·hr/mL; N-desmethylclobazam: Cmax =8090 ng/mL, AUC0-tau = 89539 ng·hr/mL
Range of Linear PK	Cmax and AUC of clobazam are linear over doses of 10, 20, and 40 mg.
Accumulation at Steady State	Steady-state plasma concentrations of clobazam are attained within 7-days of dosing and on average serum concentration of clobazam were increased by a factor of 2. N-desmethylclobazam near steady state concentrations are attained at approximately 28 days of repeated daily dosing and on average were about 8 times higher than the steady-state concentration of clobazam.
Metabolites	Metabolism of clobazam is via several CYP450 isozymes. In total, 9 metabolites have been identified and 4 others have been detected but not fully identified. In humans, primary metabolism is demethylation to form the major active metabolite, N-desmethylclobazam (via CYP 2C19, 2B6), followed by hydroxylation via 2C19,18 to 4'hydroxyclobazam and via 2C18 to form 4' hydroxyl-N-desmethylclobazam. Clobazam and N-desmethylclobazam are the major moieties in plasma; both and their respective 4'hydroxy metabolites are found in both urine and feces. Glucuronides of their dihydroxy derivatives as well as those of others comprise the moieties found excreted in urine and feces. In total, approximately 82 % and 11% of a radioactive dose of

Reference ID: 2997000

Reference ID: 2997000

Table 1. Highlights of Clobazam Clinical Pharmacology	
Description	**Result**
	clobazam has been recovered in human urine and feces, respectively
Absorption	
Absolute/Relative Bioavailability	Clobazam is rapidly and almost completely absorbed and absolute bioavailability is approximately 87% after oral administration
Tmax	Clobazam: 2 hours (range: 1-3 hr) following a single dose; 3.5 hours (range: 1-4 hr) following multiple dosing. N-desmethylclobazam: 45 hours (range: 36-120 hr) following a single dose; 2.2 hours (range: 1-4 hr) following multiple dosing.
Distribution	
Vz/F	Clobazam is highly lipophilic and distributes rapidly throughout the body. Volume of distribution following single and multiple doses ranged from ~110L to 165L.
% bound	Mean plasma protein binding of clobazam approximated 78.5 ±6.2 (SD) and is concentration independent. Plasma protein binding of N-desmethylclobazam is approximately 72.5 ± 2.5 %.
Elimination	Clobazam is highly metabolized and is eliminated primarily as metabolites in urine (82%) and in feces (11%)
Terminal ½ Life	Clobazam = 40 hr; N-desmethlyclobazam = 70 hr
CL/F or Cl	CL/F = 1.9 L/hr
Intrinsic Factors	
Age	Pharmacokinetic comparisons were made among young males (age 20-37), young females (age 18-26), elderly males (age 60-69) and elderly females (age 60-72). Clobazam was rapidly absorbed in all groups and age was not found to alter clobazam absorption pharmacokinetics. The elimination half-life was significantly longer in both male and female subjects over the age of 60 years. In elderly males, the average half-life was approximately 3-fold greater than that in young adult males. The average half-life of elderly females was approximately 1.5-fold greater than that in young adult females. The average clearance of 0.63 mL/min/kg in young males was significantly higher than the 0.36 mL/min/kg in elderly males ($p<0.05$). The clearances of 0.56 and 0.48 mL/min/kg in young versus elderly female adults, respectively, were not significantly different. The same results were found for unbound clearances after taking into account protein binding.
Sex	Pharmacokinetic comparisons were made among young males (age 20-37), young females (age 18-26), elderly males (age 60-69) and elderly females (age 60-72). Clobazam was rapidly absorbed in all groups and sex was not found to alter clobazam absorption pharmacokinetics. The average half-life of young adult females is approximately 2-fold that of young adult males. The average half-life in elderly males was approximately the same as the half-life in elderly female subjects.

Reference ID: 2997000

Table 1. Highlights of Clobazam Clinical Pharmacology	
Description	**Result**
	The clearances of 0.63 mL/min/kg and 0.56 mL/min/kg from young males versus young female adults, respectively, were not significantly different. The clearances of 0.36 mL/min/kg and 0.48 mL/min/kg from elderly males versus elderly female adults, respectively, were not significantly different. The same results were found for unbound clearances after taking into account protein binding.
Race	A formal study to evaluate an ethnic factor in the phamacokinetics of clobazam has not been conducted
Hepatic	The single dose Cmax of clobazam was decreased by approximately 32% in patients with liver disease; however, CL/F of clobazam was approximately the same between patients with liver disease and healthy subjects. The Tmax of clobazam was delayed approximately 1 hour in patients with liver disease. There were no clinically significant changes in the Cmax values of N-desmethylclobazam between the patients with liver disease and healthy subjects; however, the Tmax was delayed by approximately 40 hours in patients with liver disease or hepatic impairment.
Renal Impairment	The effect of renal impairment on clobazam pharmacokinetics is currently not known. However, a study is currently being conducted to investigate the effect of renal insufficiency on the pharmacokinetics of clobazam.
Extrinsic Factors	
Drug Interactions	
Alcohol	Administration of clobazam (20 mg) with alcohol to normal male volunteers produced an enhanced absorption of clobazam: higher serum clobazam levels (389 ± 157 ng/mL) relative without alcohol (244±87 ng/mL) (P>0.05). Systemic exposure (mean_AUC) was 98.2 ug·hr/mL with alcohol; 63.5 ug·hr/mL without.
Valproic Acid concentrations	In patients receiving concomitant cloabazam (20 mg to steady state) and valproic acid showed a slight increase in plasma valproic acid concentrations. There were no effects on clobazam
Cimetidine	Pre-treatment with cimetide, a CYP450 inhibitor, followed by concomitant 30 mg clobazam, did not effect the Tmax or Cmax of clobazam or N-desmethylclobazam, although the AUC of clobazam with cimetidine was somewhat higher (16.24 mg·hr/mL) relative to 13.88 mg·hr/mL without. In another study examining the effects of cimetidine on the single doses of clobazam and Ndesmethylclobazam (30 mg clobazam, 30 mg N-desmethylclobazam, 400 mg cimetidine), the AUC of clobazam was increased

Table 1. Highlights of Clobazam Clinical Pharmacology	
Description	**Result**
	approximately 65%; for N-desmethylclobazma, the AUC was increased approximately 83.5%.
Felbamate	Administration of clobazam with felbamate (a CYP450 inducer) resulted in a 2-fold decrease in plasma concentrations of clobazam with a 5-fold increase in N-desmethylclobazam plasma concentrations
Standard AEDs	In population PK studies, concomitant clobazam (10 or 20 mg) with carbamazepine, phenobarbital, phenytoin and valproic acid to epileptic patients had either no effect or tended to decrease plasma levels from up to approximately 65%.
Food Effect	Food did not have a clinically significant effect on overall (approximately 1% increase) or maximum (approximately 20% decrease) plasma exposure on clobazam and N-desmethylclobazam. Clobazam: Mean Tmax was 2 hour (range: 1-3 hr) in a fasted state; the Mean Tmax was 3 hours (range: 1-8 hr) in presence of food. N-desmethylclobazam: Mean Tmax was 48 hour in presence of food; the Mean Tmax was 42 hour in a fasted state.
Expected high Clinical Exposure Scenario	The major expected adverse events from the supratherapeutic dose are constipation, headache, dizziness, somnolence, and anxiety. Given linear pharmacokinetics, the supratherapeutic dose to be used in the TQT study of 160 mg is 4 times the maximum single dose (40 mg) to be tested in the LGS trials and the Cmax and AUC should be proportional. At 160 mg/day, Cmax if dosed BID is predicted to be 3091 ng/mL; AUC is predicted to be 26092 ng·hr/mL

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/s/

JOANNE ZHANG
08/08/2011

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KEVIN M KRUDYS
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08/09/2011

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: July 25, 2011

TO: Su-Lin Sun, PharmD, Regulatory Health Project Manager
Phil Sheridan, M.D., Medical Officer
Division of Neurology Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Jean Mulinde, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202-067

APPLICANT: Lundbeck Inc.

DRUG: Onfi (Clobazam)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of seizures associated with Lennox-Gastaut Syndrome

CONSULTATION REQUEST DATE: February 11, 2011

DIVISION ACTION GOAL DATE: October 23, 2011

PDUFA DATE: October 23, 2011

I. BACKGROUND:

Clobazam is a 1,5-benzodiazepine with sedative, anxiolytic, muscle relaxant, and anticonvulsant properties. It is marketed in most of the world by Sanofi-Aventis under the tradename Frisium for the treatment of anxiety and epilepsy, but it is not approved in the United States (U.S.). In 2004, Ovation Pharmaceuticals obtained marketing rights for clobazam in the U.S, Canada, and Mexico from Sanofi-Aventis. Ovation initiated development of clobazam for the treatment of seizures associated with Lennox-Gastault Syndrome (LGS) in 2005 under IND 70,125. Ovation was subsequently acquired by Lundbeck, Inc.

The pending NDA provides for an immediate release clobazam tablet formulation in three strengths: 5 mg, 10 mg, and 20 mg. The investigational product is intended to be used as an adjunctive treatment of seizures associated with LGS in children over 2 years of age. The recommended doses, depending on age and body weight, are between 10mg/day and 40 mg/day given in two divided doses. The investigational product may be administered by crushing and mixing with food such as applesauce.

Lundbeck, Inc submitted this application for the use of clobazam in the treatment of young children suffering from seizures associated with LGS. Two clinical trials were submitted in support of the application: Study OV-1002 and Study OV-1012.

Colbazam is a benzodiazepine used in the treatment of anxiety disorders and epilepsy and is being studied in the U.S. for the treatment of seizures associated with Lennox-Gastaut Syndrome. Lennox-Gastaut Syndrome is a severe childhood epileptic encephalopathy characterized by a slow spike and wave electroencephalogram (EEG) and multiple seizure types, and is usually associated with an abnormal developmental state and behavioral disturbances.

According to the Applicant, clobazam may provide an improved safety profile compared to other anti-epilepetic drugs (AEDs) currently approved for the treatment of LGS and may cause less hypotonia and drooling than other benzodiazepines.

Protocol OV-1002

The objective of this study was to evaluate the safety and efficacy of clobazam in the treatment of seizures which lead to drop attacks (drop seizures) in subjects 2 to 30 years of age with LGS.

The primary endpoint was the percent reduction in the number of drop seizures (average per week) from the 4-week baseline period compared to the 4-week maintenance period as obtained from the seizure diaries. The key secondary efficacy endpoint was the percent of subjects considered treatment responders defined as those with a 25%, 50%, or 74% reduction

in drop seizures from the 4-week baseline period compared to the 4–week maintenance period.

Protocol OV-1012

This Phase III trial of clobazam was a multicenter, randomized, double-blind and placebo-controlled, parallel-group study designed to assess the safety and efficacy of clobazam as adjunctive therapy in subjects with LGS.

The primary efficacy objective of this study was to determine the efficacy of clobazam in the reduction of drop seizures at 3 dose levels when compared to baseline during 12 weeks maintenance dosing in a placebo-controlled trial in subjects with LGS. A key secondary objective was to determine the efficacy of clobazam as determined by responder rates and global evaluation of subject symptoms.

Subjects 2-60 years of age weighing >12.5 kg and currently receiving 1-3 AEDs were eligible for screening if they met the LGS diagnostic inclusion criteria, including having experienced > 2 drop seizures per week during the 4-week baseline period, and did not meet any exclusion criteria. Qualifying subjects must have been <11 years of age at the onset of LGS and must have weighed more than 12.5 kg. No subjects < 11.0 kg were to be enrolled. Female subjects were to use adequate birth control. Subjects must provide informed consent and must not participate in other clinical trials for the duration of this trial.

The primary efficacy endpoint was the percent reduction in the number of drop seizures (average per week) from the 4-week baseline period compared to the 12–week maintenance period. A drop seizure is defined as a drop attack or spell involving the entire body, trunk, or head that led to a fall, injury, slumping in chair, or head hitting a surface or that could have led to a fall or injury, depending on the position of the subject at the time of the attack or spell.

The review division requested inspection of 4 clinical investigators for the two pivotal protocols (4 sites; 1 foreign site and 3 domestic sites to cover Study 0V-1002 and OV-1012) as data from the two protocols are considered essential to the approval process. These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects, and 2) relatively high number of site specific protocol violations. Lundbeck, Inc. is the Applicant for this application.

II. RESULTS (by protocol/site):

Name of CI, site # and location	Protocol and # of subjects	Inspection Dates	Final Classification
Joan Conry, M.D. Dept. of Neurology Children's Hospital 111 Michigan Ave. NW Washington, DC 20010 Site# 003	Protocol OV-1002 Number of subjects: 10	4/4-4/8/2011	NAI
Juliann Paolicchi, M.D. Dept. Of neurology Children's Hospital 700 Children's Drive Columbus, OH 43205 Site# 018	Protocol OV-1002 Number of subjects: 8	4/14-4/20/2011	NAI
Yu-Tze Ng, M.D. Barrow Neurological Institute Children's Health Center 500 West Thomas Rd, Suite 400 Phoenix, AZ 85013 Site# 008	Protocol OV-1012 Number of subjects: 18	3/21-4/21/011	VAI
Anaita Hedge, M.D. Jaslok Hospital and Research Centre Mumbai, Maharashtra India Site# 817	Protocol OV-1012 Number of subjects: 10	5/30-6/3/2011	Pending Preliminary: VAI

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Note: Observations noted below for one site (Dr. Anaita Hedge) are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

Protocol Study OV-1002

1. **Joan Conry, M.D.**
   Washington, DC 20010

   a. What Was Inspected: At this site, a total of 11 subjects were screened, and one subject was reported as a screen failure. Ten (10) subjects were randomized, and 10 subjects completed the study. Review of Informed Consent Documents for all subject records, verified that subjects signed prior to enrollment.

   A review of the medical records/source documents was conducted. The medical records for four randomly selected subjects were reviewed in detail, including drug accountability records, vital signs, laboratory test results, IRB records, and use of concomitant medications. Source documents were compared to case report forms and to data listings, to include primary efficacy endpoints and adverse events.

   b. **General observations/commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Conry. The medical records reviewed were found to be in order and the data verifiable. There were no deaths and no under-reporting of adverse events. There were no known limitations to the inspection. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the pending application.

   c. Assessment of Data Integrity: The data, in support of clinical efficacy and safety at Dr. Conry's site are considered reliable and appear acceptable in support of the pending application.

2. **Juliann Paolicchi, M.D.**
   Colombus, OH 43205

   a. What Was Inspected: At this site, a total of 35 potential subjects were interviewed and many parents declined participation in the study. Eleven (11) subjects were screened, and 3 subjects were reported as screen failures. Eight (8) subjects were randomized and completed the study. Seven subjects opted to continue on the long term phase of the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment. The subjects who continued on the long term treatment were all re-consented.

   The medical records/source data for all subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, and inclusion/exclusion criteria. Source documents were compared to CRFs and data listings for primary efficacy endpoints and adverse events listing.

b. General Observations/Commentary: The clinical investigator was no longer at the site; however, a sub-investigator for the study, Dr. Tsao, was available and served as the most responsible party at the site for the study during the inspection. At the conclusion of the inspection, no Form FDA 483 was issued. The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection since the sub-investigator and the clinical coordinator were able to provide the necessary documents and answers to questions raised by the FDA investigator. There were no deaths and no under-reporting of adverse events. The study appears to have been conducted adequately, and the data generated by this site can be used to support the pending application.

c. Assessment of Data Integrity: The data, in support of clinical efficacy and safety at Dr. Paolicchi's site are considered reliable and appear acceptable in support of the pending application.

Protocol Study OV-1012

3. **Yu-Tze Ng, M.D.**
   Phoenix, AZ 85013

a. What Was Inspected: At this site, a total 22 subjects were screened, one subject was reported as a screen failure, 22 subjects were randomized into the study, and 3 subjects withdrew consent and were discontinued from the study. Eighteen (18) subjects completed the study and re-consented to enroll in the long term phase of the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for 18 subjects were reviewed for drop seizure diaries for all visits. The medical records for eight subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, and use of concomitant medications. Source documents for subjects were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events

b. General Observations/Commentary: At the conclusion of the inspection, a 2 item Form FDA 483 was issued to Dr. Ng. Our investigation found protocol violations and inadequate record keeping.

Protocol Violations:

Review of source documents revealed the clinical investigator did not adhere to the protocol. For example,

- Subjects 7025 and 7027 did not have 28 days of daily seizure diary data documented as required by the protocol. The protocol required the baseline

period to be 28 days of seizure diary data. The two subjects had a baseline documentation periods of only 26 and 18 days, respectively.

- The protocol required the EKGs to be completed prior to blood draws. For certain subjects the EKGs were performed after blood draws which is contrary to the protocol.
- Subjects 8024 and 8015 did not sign the most recent approved informed consent document.

Record Keeping Violations:

Review of source documents revealed the clinical investigator did not maintain adequate and accurate records which included, but was not limited to the following:

- Discrepancies in seizure counts between source documents and what was recorded on the case report forms for a few subjects. For example, Subject 7009 actual seizure count marked was 16, but the eCRF listed 14.
- Discrepancies in seizure counts between source documents and what was recorded on the case report form for Subject 8094 for certain visits. For example, for Week 1 the Single Drop Seizure total daily count was 3 and the eCRF listed 8. For Week 5, the Single Drop Seizure total daily count was 6 and the eCRF listed 9.
- Minor discrepancies in vital signs readings between source documents and what was recorded on the case report forms for a few subjects. For example, Subject 7128 on the Week 9 source document had recorded a pulse rate of 92 bpm and a blood pressure of 100/62 mmHg while the eCRF listed a pulse rate of 90 bpm and a blood pressure of 100/77mmHg.
- The source document for Subject 8006, for the Neurological Examination under Gait and Station was marked "abnormal NCS, unsteadiness". The eCRF showed Gait and Station as normal. A similar observation was found for Week 15, in that the source document listed "coordination, abnormal NCS, Mildly Ataxic fingers-to-nose" while the eCRF showed coordination as normal.

The clinical investigator acknowledged the inspectional findings in a written response dated May 10, 2011, in which he promised to implement corrective actions to prevent the recurrence of the inspectional findings in future studies. OSI finds his response acceptable.

c. Assessment of Data Integrity: Although regulatory violations were noted, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect on overall data integrity to be significant. In general, the records reviewed were found to be verifiable with the exceptions as noted above. There were no known limitations to this inspection. The data generated from Dr. Ng's site are considered reliable and appear acceptable in support of the application.

4. Anaita Hedge, M.D.
Mumbai, India

a. What was Inspected: At this site, a total 10 subjects were screened, 10 subjects were randomized, and all 10 subjects completed the study. Review of Informed Consent Documents, for all subjects, verified that all subjects signed consent forms prior to enrollment.

The medical records/source data for 10 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, diary cards, IRB files, prior and current medications, inclusion/exclusion criteria, the use of concomitant medications; source documents for the 10 subjects were compared to case report forms and to data listings for primary efficacy endpoint and adverse events.

b. General Observations/Commentary: At the conclusion of the inspection, a two item Form FDA 483 was issued to Dr. Hedge. Our investigation found protocol deviations and inadequate record keeping.

Protocol Violations:

- The clinical investigator did not complete all visit procedures or assessments within the study window for two subjects (81703 and 81708). Subject 81701 was identified as missing the Day -1 window by four days. Subject 81708 was out of window for Visit 6 by 3 days.

Inadequate Drug Accountability:

- The clinical investigator did not maintain adequate records of the disposition of the drug. The clinical investigator stated that the tablet count reconciliation was performed by the site, but these counts were not included in the investigational return/request forms. In addition, the clinical investigator stated that the sponsor confirmed the returned tablet count.

The clinical investigator acknowledged the inspectional findings in a written response dated June 17, 2011, in which he promised to implement corrective actions to prevent the recurrence of the inspectional findings in future studies. OSI finds his response acceptable.

The medical records reviewed disclosed no other adverse findings that would negatively impact the reliability of the data. With the exception of the items noted above, the records reviewed were found to be organized and the data verifiable. There were no known limitations to this inspection.

c. Assessment of Data Integrity: Although regulatory violations were noted, the findings are considered isolated in nature and unlikely to significantly impact data reliability. The data from Dr. Hedge's site are considered reliable and appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Four clinical investigator sites, three domestic and one foreign, were inspected in support of this application. The inspections of Drs. Conry and Paolicchi revealed no regulatory violations and the final classification for these inspections is No Action Indicated (NAI). While regulatory violations were identified during the inspections of Dr. Ng and Hedge, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect on overall data integrity to be significant. The final classification for the inspection of Dr. Ng is Voluntary Action Indicated (VAI) and the preliminary classification for the inspection of Dr. Hedge is also VAI. Overall, the data submitted from these sites are considered acceptable in support of the pending application.

Note: Observations noted above for Dr. Hedge's site inspection are based on an e-mail communication from the field; the EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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Susan Thompson, M.D.
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Jean Mulinde, M.D.
Acting Branch Chief
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Office of Compliance (CDER)

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/s/

ANTOINE N EL HAGE
07/27/2011

SUSAN D THOMPSON
07/27/2011

JEAN M MULINDE
07/27/2011

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

Date:	May 26, 2011
Application Type/Number:	NDA 202067
To:	Russell Katz, Director Division of Neurology Products
Through:	Melina Griffis, RPh, Team Leader Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Lubna Merchant, M.S., Pharm.D, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name and Strength:	Onfi (Clobazam) Tablets, 5 mg, 10 mg, and 20 mg.
Applicant/sponsor:	Lundbeck Inc.
OSE RCM #:	2011-189

CONTENTS

Reference ID: 2952647

1. INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis evaluation of the proposed labels and labeling for Onfi (Clobazam) Tablets NDA 202067 for areas of vulnerabilities that could lead to medication errors. The proposed proprietary name is evaluated under separate review (OSE # 2011-1089).

2. METHODS AND MATERIALS

Using Failure Mode and Effects Analysis (FMEA)[1], the Division of Medication Error Prevention and Analysis (DMEPA) evaluates the container labels, and insert labeling. This review focuses on labels and labeling submitted as part of the December 23, 2010 original NDA submission. See Appendix A for images of the proposed container labels.

3. RESULTS

The following section describes the results of our label and labeling review.

3.1 LABELS AND LABELING

The container label risk assessment findings indicate the presentation of information on the label does introduce vulnerability to confusion that can lead to medication errors. It was determined that the labels and labeling need improved differentiation between the proposed strengths. We provide labeling recommendations in section 5 to address this deficiency.

4. CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling identified areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations in Section 4.1 Comments to the Applicant for the container labels. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Laurie Kelley at 301-796-5068.

4.1 COMMENTS TO THE APPLICANT:

A. General comments

We remind the Applicant of their requirement to comply with 21 CFR 208.24. We acknowledge the use of a Medication Guide statement. Please ensure that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose.

Reference ID: 2952647

B. Proposed Container Label (All sizes and strengths)

1. The proposed labels for all three strengths utilize (b) (4)

2. Revise the presentation of the established name to 'Clobazam' and ensure that it has equal prominence to the 'Tablets' statement.

C. Proposed Carton Labeling (All sizes and strengths)

1. See comment B1 and B2 above.

2. We note that the control substance symbol is prominently displayed next to the strength presentation and is distracting. Relocate the control substance symbol to appear away from the strength presentation.

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

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/s/

LUBNA A MERCHANT
05/26/2011

MELINA N GRIFFIS
05/26/2011

CAROL A HOLQUIST
05/27/2011

DSI CONSULT: Request for Clinical Inspections

Date: February 9, 2011

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Antoine El-Hage, PhD
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Phil Sheridan.MD / DNP Clinical Reviewer
Norman Hershkowitz, MD. /DNP TL

From: Su-Lin Sun, PharmD. Regulatory Project Manager/DNP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA202067 Onfi (Clobazam) tablet
Applicant/ Applicant contact information (to include phone/email):
Ms. Jenny Swalec
Sr. Director, Global Regulatory Affairs
Lundbeck, Inc.
4 Parkway North, Suite 200
Deerfield, IL 60015
Phone # (847) 282-1066
Email: JSWA@Lundbeck.com

Drug Proprietary Name: Onfi
NME or Original BLA (Yes/No): yes (NME)
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): yes
Is this for Pediatric Exclusivity (Yes/No): Yes

Proposed New Indication(s): adjunctive treatment for seizures associated with Lennox-Gastaut syndrome (LGS) in children ≥ 2 years of age.

PDUFA:
Action Goal Date: October 23, 2011
Inspection Summary Goal Date: August 23, 2011

Reference ID: 2905741

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
003 Joan A Conry, MD Dept of Neurology Children's National Medical Center 111 Michigan Ave, NW Washington, DC 20010 202-884-2120 jconry@cnmc.org	OV 1002	10	Lennox-Gastaut Syndrome
018 Juliann Paolicchi, MD Dept of Neurology Children's Hospital 700 Children's Drive Columbus, OH 43205 614-722-4605	OV 1002	8	Lennox-Gastaut Syndrome
008 Barrow Neurological Institute Children's Health Center St. Joseph's Hospital 500 West Thomas Road, Suite 930 Phoenix, AZ 85013 602-406-3800 y2ng@chw.edu	OV 1012	18	Lennox-Gastaut Syndrome
817 Anaita Hegde, MD Jaslok Hospital and Research Centre Mumbai, Maharashtra INDIA	OV 1012	10	Lennox-Gastaut Syndrome

III. Site Selection/Rationale

The selected sites had the most pronounced positive efficacy effects and the largest enrollment.

Rationale for DSI Audits

Domestic Inspections:

Reasons for inspections (please check all that apply):

__x__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
__x__ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__x__ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable): N/A

Should you require any additional information, please contact *Su-Lin Sun (RPM*) at *301-796-0036 or Phil Sheridan (DNP Medical Officer)* at 301-796-1145.

Concurrence: (as needed)

Dr. Norman Hershkowitz Medical Team Leader
Dr. Phil Sheridan Medical Reviewer
Dr. Russell Katz Division Director (for foreign inspection requests or requests for 5 or more sites only)

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

/s/

SU-LIN SUN
02/15/2011

RUSSELL G KATZ
02/16/2011