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MEDICAL REVIEW(S)

CLINICAL REVIEW

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(Proposed) Trade Name	Onfi
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Applicant	Lundbeck
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Intended Population(s)	Lennox-Gastaut Syndrome Patients \geq 2 years of age with Lennox-Gastaut Syndrome

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients age 2 years of age and above.

1.2 Risk Benefit Assessment

Lennox-Gastaut syndrome (LGS) is a severe childhood epileptic encephalopathy characterized by a slow spike and wave electroencephalogram (EEG), multiple seizure types, and usually an abnormal developmental state and behavioral disturbances. Recurrent episodes of status epilepticus may occur. Onset of LGS, as determined by the appearance of the characteristic seizures, generally occurs between 3 and 8 years of age, with peak occurrence between 3 and 5 years. Most patients continue to have refractory epilepsy and neurocognitive impairment that persist into adulthood.

Lennox-Gastaut syndrome is characterized by multiple seizure types, predominantly of the tonic, atonic, and atypical absence variety. Pharmaceutical agents that show improvement in the most debilitating variety of seizures, drop seizures, are particularly desirable in this population. A drop seizure is defined as a drop attack or spell involving the entire body, trunk, or head that leads to a fall, injury, slumping in chair, or head hitting surface or that could have led to a fall or injury, depending on the position of the patient at the time of seizure onset. These drop attacks lead to significant head trauma and necessitate the wearing of a protective helmet. Drop attacks, which may occur as a result of tonic, atonic or myoclonic seizures, are particularly disabling to patients with LGS, and indeed the falls pose a safety hazard to patients. These drop attacks occur in about 56% of patients who have slow spike and wave on EEG.

Lennox-Gastaut syndrome poses a significant treatment challenge. No single antiepileptic drug (AED) provides satisfactory relief for all or most subjects with LGS, and a combination of treatments is often required. Even with combination therapy, many LGS subjects show resistance to treatment. Adjunctive therapy with newer anticonvulsant medications has demonstrated efficacy for some subjects, although polytherapy and high medication doses are often associated with unfavorable adverse event profiles. Currently, six antiepileptic drugs (AEDs) (clonazepam, felbamate, lamotrigine, topiramate, rufinamide, and clobazam [Onfi] tablets) have demonstrated clinical efficacy and are approved by the Agency for the treatment of LGS. Despite the availability of these approved treatments, many patients with LGS continue to be refractory to treatment. More effective and better tolerated treatment options are needed for this population.

The efficacy studies previously reviewed under NDA 202067 demonstrated that clobazam (Onfi) tablet form is effective at tolerable doses in reducing the number of both intractable drop and non-drop seizures associated with LGS. Clobazam had been marketed for forty years in many other countries so its adverse event profile was known to be similar to other benzodiazepines, such as clonazepam which was already approved in the United States for adjunctive treatment of seizures associated with LGS. The efficacy appeared to persist for most patients despite the known tendency for patients to develop tolerance to benzodiazepines.

Therefore clobazam tablets were approved for adjunctive treatment of seizures associated with LGS on October 21, 2011.

Clobazam (Onfi) oral suspension is proposed for use in patients who have difficulty swallowing whole or crushed tablets due to young age or the neurological disability associated with LGS. The bioavailability study demonstrates that the bioavailability of the oral suspension is equivalent to that of the currently approved tablet form. Therefore, the benefits of approval of clobazam oral suspension outweigh the risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None from Clinical review.

No REMS were necessary for Clobazam tablets (NDA 202067). There is a non-REMS medication guide (as with all antiepileptic drugs) for Clobazam tablets which will be updated to include the oral suspension if approved.

1.4 Recommendations for Postmarket Requirements and Commitments

None from Clinical Review.

Existing non-clinical PMRs for Clobazam tablets (NDA 202067) to further characterize carcinogenesis and teratogenesis will have results applicable to Clobazam oral suspension.

2 Introduction and Regulatory Background

2.1 **Product Information**

Clobazam is a 1, 5–benzodiazepine approved for the treatment of anxiety disorders, epilepsy, and similar indications in over 80 other countries worldwide. The tablet form of clobazam (Onfi) was approved in the United States for adjunctive treatment of seizures associated with LGS on October 21, 2011.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, six AEDs (clonazepam, felbamate, lamotrigine, topiramate, and rufinamide, and clobazam [Onfi) tablets] have demonstrated clinical efficacy and are approved by the Agency for the treatment of LGS. Despite the availability of these approved treatments, many subjects with LGS continue to be refractory to treatment. More effective and better tolerated treatment options are needed for this population of medically intractable epilepsy subjects.

Drug name	Drug class
clonazepam	benzodiazepine
felbamate	dicarbamate
lamotrigine	phenyltriazine
topiramate	sulfamate
rufinamide	triazole
clobazam	benzodiazepine
(tablet)	

Table 1 Current Treatments for LGS

2.3 Availability of Proposed Active Ingredient in the United States

Already marketed in tablet form.

2.4 Important Safety Issues With Consideration to Related Drugs

Intravenous benzodiazepines used acutely for status epilepticus may cause respiratory and cardiovascular depression. With chronic oral use, the benzodiazepines produce sedation, drowsiness, lightheadedness, ataxia, cognitive slowing, headache, vertigo, and gastrointestinal symptoms. There is also a risk for the development of tolerance to efficacious effect. Abrupt withdrawal benzodiazepines may cause seizures, insomnia, psychiatric symptoms, or delirium tremens

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Clobazam was first approved in 1970 in Australia (international birth date) and has also been approved for the treatment of anxiety and/or the adjunctive treatment of epilepsy in over 100 countries.

In the U.S., an IND was filed on 25 May 2005 by Lundbeck Inc. (Lundbeck) (formerly Ovation Pharmaceuticals); the company was notified by the Division of Neurology Products on 24 June 2005 that clinical studies with clobazam under IND 70,125 could proceed. A Type B, End of Phase 2 (EOP2) meeting was held with the Division on 09 May 2007 to discuss the results obtained from the completed Phase 2 study, OV -1002, and to discuss planning for the pivotal Phase 3 study (OV-1012) and preparation for filing a U.S. NDA (NDA 202067).

During the EOP2 meeting for NDA 202067, the Agency expressed concern about the potential for patients developing tolerance to benzodiazepines, thus leading to a lack of long-term efficacy. To address this possibility, the Maintenance Phase for the pivotal Phase 3 study (OV-1012) was lengthened from 8 to 12 weeks.

Lennox-Gastaut syndrome (LGS) is estimated to represent 1 % to 2% of all childhood epilepsy cases. Therefore, LGS affects fewer than 200,000 people in the United States (US), and in accordance with Code of Federal Regulations (CFR) 21CFR 316.20, qualifies as an orphan indication. On 24 August 2007, Lundbeck submitted an Orphan Drug Application requesting Orphan Drug Designation for clobazam. Orphan drug designation was awarded on 18 December 2007.

After review of NDA 202067, Clobazam (Onfi) in tablet form was approved for adjunctive treatment of seizures associated with LGS on October 21, 2011.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The bioavailability study has been conducted and reported with adequate quality and integrity.

3.2 Compliance with Good Clinical Practices

The bioavailability study is compliant with Good Clinical Practices.

3.3 Financial Disclosures

This NDA is supported by only one study, the bioequivalence study 176-808-2012.

The Sponsor certified on Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) that the sole Clinical Investigator (Axel Juan, MD at Sea View Research, Miami, Florida) had not entered into any financial arrangement with the Sponsor and has no proprietary interest in the product or significant equity in the Sponsor. The Sponsor further certified that this investigator received no significant payments of other sorts as defined in 21 CFR 54.2(f).

Reviewer Note:

It appears that the investigator, Dr. Juan, has no financial conflicts of interests that might bias the study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Review pending.

1.2 Clinical Microbiology

CMC reviewer found no issues.

4.3 Preclinical Pharmacology/Toxicology

Clobazam tablets approved under NDA 202067.

4.4 Clinical Pharmacology

Clobazam tablets approved under NDA 202067.

Review by Dr. Ta-chen Wu found bioequivalence in the fasting state between the tablet and oral suspension forms.

5 Sources of Clinical Data

No new efficacy data has been submitted since the approval of Onfi (clobazam) tablets on October 21, 2011 (NDA 202067). The bioavailability study (Study 176-808-2012) demonstrates that the bioavailability of the oral suspension is equivalent to that of the currently approved tablet form.

5.1 Tables of Studies/Clinical Trials

Objectives Stuc	dy lo	est products;	Number	Duration of
Desi	ign do	losage regimens	of	therapy
			subjects	
			exposed	
Assess the relative Ope bioavailability, safety, labe and tolerability of a single 20 mg oral dose of clobazam administered as a suspension compared to a CLB 20	en C el, m ta 20 or	Compared single 20 ng oral dose in ablet form to single 20 mg oral dose in oral suspension	30 healthy adults	Single dose of each preparation with 14 day washout period

Table 2 Study 176-808-2012 Summary

5.2 Review Strategy

The clinical pharmacology reviewer has reviewed the bioequivalence study (Study 176-808-2012). I focused my review on the safety data from Study 176-808-2012.

5.3 Discussion of Individual Studies/Clinical Trials

The bioavailability study (Study 176-808-2012) is the only study in this NDA.

Study Objectives:

Primary Objective

• to assess the relative bioavailability of a single 20 mg oral dose of CLB administered as a suspension as compared to a CLB 20 mg oral tablet $(1 \times 20 \text{ mg})$

Secondary Objectives

• to investigate the safety and tolerability of single oral doses of CLB 20 mg suspension compared to CLB 20 mg tablet $(1 \times 20 \text{ mg})$

• to compare the pharmacokinetic profile of CLB and N-CLB following single oral doses of CLB 20 mg suspension compared to CLB 20 mg tablet (1 × 20 mg)

Study Design:

This was a single-center, randomized, open-label, 2-way crossover, single-dose study designed to evaluate the bioavailability of CLB from a suspension (test) relative to that from a tablet (reference).

Thirty adult men and women in good health were selected according to the selection criteria for study participation.

The subjects were randomly assigned in equal numbers to 2 sequences of the 2 study formulations according to a randomization schedule.

There was a 14 day washout period between the dose administrations.

Subjects were screened up to 21 days prior to study drug administration and fasted overnight prior to study drug administration. Subject confinement began the day prior to dosing (Day -1 for Period 1 and again on Day 14 for Period 2) and continued for 7 days and 6 nights in each study period. Subjects were discharged following the 120 hour blood collection (Day 6 of Period 1 and Day 20 of Period 2).

Blood samples were taken pre-dose (0 hour) to 312 hours post dosing in both Periods 1 and 2. Subjects returned to the clinical site for blood sample collections on the mornings of Days 8, 10, 12, and 14 (Period 1) and Days 22, 24, 26, and 28 (Period 2) for the collection of the remaining blood samples.

The sampling scheme used ensured that for the majority of subjects, at least 80% of the AUC from zero to infinity (AUC0-inf) was derived from non-extrapolated data.

Pharmacokinetic Results:

Absorption of CLB occurred more rapidly after suspension administration than after tablet administration. Mean Cmax and median tmax for CLB were 421 ng/mL at 0.75 hours following the suspension administration and 354 ng/mL at 2.00 hours following the tablet administration.

Mean t1/2 values for CLB were 39.7 and 38.9 hours following the suspension and tablet administration, respectively. Both CL/F and VZ/F of CLB were similar between treatments.

Bioequivalence testing showed that the suspension/tablet ratio point estimate and 90% Cls of this ratio for CLB were: Cmax = 1.19 (1.12 to 1.27); AUC0-t = 0.997 (0.977 to 1.02); and AUC0-inf = 0.995 (0.976 to 1.01). Thus, bioequivalence criteria were met for AUC0-inf and AUC0-t; however, for Cmax the upper band of the 90% CI was 1.27 instead of the accepted value of 1.25.

Following a single oral dose of 20 mg CLB suspension or 20 mg CLB tablet, the metabolite, N-CLB, slowly appeared in plasma (median tmax value of 48.0 hours for both treatments) and was eliminated (mean t1/2 values of 59.5 and 72.3 hours, respectively). The exposure of N-CLB was similar between the tablet and suspension formulations.

The bioavailability study (Study 176-808-2012) demonstrates that the bioavailability of the oral suspension is equivalent to that of the currently approved tablet form for clobazam and its active metabolite nor-clobazam.

6 Review of Efficacy

Efficacy Summary

No new efficacy data has been submitted since the approval of Onfi (clobazam) tablets on October 21, 2011 (NDA 202067). The bioavailability study (Study 176-808-2012) demonstrates that the bioavailability of the oral suspension is equivalent to that of the currently approved tablet form.

7 Review of Safety

Safety Summary

Clobazam has been previously approved in tablet form for the same indication (NDA 202067). Preclinical and clinical studies of safety are summarized in current labeling.

The following is a summary of the safety and tolerability data from the open-label bioavailability study (Study 176-808-2012) described in section 5 of this review.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The bioavailability study (Study 176-808-2012) is the only study in this NDA.

Safety was evaluated on the basis of adverse events, clinical safety laboratory tests, vital signs, weight, ECGs, physical and neurological examinations, and C-SSRSs.

Blood samples for plasma CYP2C19 genotyping collected on Day 1 (predosing) confirmed that none of the 30 subjects were poor metabolizers due to abnormalities of the CYP2C19 isoenzyme.

7.1.2 Categorization of Adverse Events

Adverse Event Definitions

Adverse event – is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Serious adverse event– is any adverse event that: • results in death

• is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe)

- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

• is medically important (this refers to an event that may not be immediately lifethreatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent any of the SAEs defined above)

Non-serious adverse event – is any adverse event that does not meet the definition of an SAE.

Intensity

The investigator assessed the intensity of an adverse event using the following definitions:

• Mild – the adverse event causes minimal discomfort and does not interfere in a significant manner with the subject's normal activities.

• Moderate – the adverse event is sufficiently uncomfortable to produce some impairment of the subject's normal activities.

• Severe – the adverse event is incapacitating, preventing the subject from participating in his/her normal activities.

Causality

The investigator assessed the causal relationship between an adverse event and the IMP using the following definitions:

Probable – the adverse event has a strong temporal relationship to the IMP or recurs on rechallenge, and another etiology is unlikely or significantly less likely.
Possible – the adverse event has a suggestive temporal relationship to the IMP, and an alternative etiology is equally or less likely.

• Not related – the adverse event has no temporal relationship to the IMP or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the IMP and the adverse event).

An adverse event is considered causally related to the use of the IMP when the causality assessment is probable or possible.

Assessment of Outcome

The investigator assessed the outcome of an adverse event using the following definitions:

- Recovered the subject has recovered completely, and no symptoms remain.
- Recovering the subject's condition is improving, but symptoms still remain.
- Recovered with sequelae the subject has recovered, but some symptoms remain (for example, the subject had a stroke and is functioning normally, but has some motor impairment).

• Not recovered – the subject's condition has not improved and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).

- Death
- 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable. Only one study.

7.2 Adequacy of Safety Assessments

Clobazam has been previously approved in tablet form for the same indication (NDA 202067). Preclinical and clinical studies of safety are summarized in current labeling.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in Bioavailability Study 14033A.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events occurred.

7.3.3 Dropouts and/or Discontinuations

No dropouts and/or discontinuations due to an adverse event occurred.

All 30 subjects randomized completed the study.

7.3.4 Significant Adverse Events

No significant adverse effects were reported in the study.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results7.4.1 Common Adverse Events

Table 3 Summary of Adverse Events by Treatment (from Sponsor's CSR Panel15)

	Treatment A (N=30)	Treatment B (N=30)
Subjects with pre-treatment adverse events	0	0
Subjects with adverse events	2 (6.7)	2 (6.7)
Subjects with SAEs	0	0
Subjects with adverse events leading to withdrawal	0	0
Total number of adverse events	3	2

Note: Treatment A: 20 mg CLB suspension; Treatment B: 20 mg CLB tablet.

Treatment A was the test formulation, and Treatment B was the reference formulation.

A total of 5 adverse events were reported during the study. No adverse event occurred in more than 1 subject. There was no apparent difference in the incidence of adverse events following 20 mg CLB suspension (test) or 20 mg CLB tablet (reference). Two (6.7%) subjects had 3 adverse events after receiving CLB suspension and 2 (6.7%) subjects had

2 adverse events after receiving a CLB tablet. No additional adverse events occurred at the time of Cmax associated with suspension formulation.

The majority of adverse events were mild, with 2 mild events being reported following each of the treatments. One moderate adverse event, presyncope, was reported following 20 mg CLB suspension, which was considered not related to the IMP by the investigator. No severe adverse events were reported in the study. The majority of adverse events were considered to be not related to the IMP by the investigator; 1 adverse event of dizziness was considered to have a probable relationship, and 1 adverse event of abdominal pain was considered to have a possible relationship to the IMP. The Investigator felt that though there was a temporal relationship to the onset of the abdominal pain symptoms and the study drug, it was equally likely that the pain may have an alternate etiology such as diet or psychosocial factors.

No pre-treatment adverse events were reported. The incidence of all adverse events is summarized in Table 4.

Table 4 Summary of Adverse Events by Preferred Term and Treatment (fromSponsor's CSR Panel 16)

	Number of Subjects (% Subjects) with Adverse Events		
Preferred Term	Treatment A (N=30)	Treatment B (N=30)	
Abdominal pain	1 (3.3)		
Bronchitis		1 (3.3)	
Dizziness		1 (3.3)	
Presyncope	1 (3.3)		
Pruritus generalised	1 (3.3)		

Note: Treatment A: 20 mg CLB suspension; Treatment B: 20 mg CLB tablet.

Treatment A was the test formulation, and Treatment B was the reference formulation.

7.4.2 Laboratory Findings

The clinical safety laboratory tests are summarized in Table 5.

Table 5 Clinical Safety Laboratory Tests (from Sponsor's CSR Panel 7)

Haematology ^a	Liver ^b	Urine ^d		
B-haemoglobin	S-total bilirubin	U-protein (dipstick)		
B-erythrocytes	S-alkaline phosphatase	U-glucose (dipstick)		
B-haematocrit	S-alanine aminotransferase	U-blood (dipstick)		
B-total leucocyte count	S-aspartate aminotransferase	U-ketones (dipstick)		
B-neutrophiles (% of total leucocytes)	S-gamma-glutamyl transferase			
B-eosinophiles (% of total leucocytes)				
B-basophiles (% of total leucocytes)				
B-lymphocytes (% of total leucocytes)				
B-monocytes (% of total leucocytes)				
B-thrombocyte count				
Lipids ^b	Kidney ^b	Serology		
S-cholesterol (total)	S-creatinine	S-HIV		
S-triglycerides	B-urea nitrogen	S-HBsAg		
	_	S-anti-HCV		
Nutritional ^b	Electrolytes	Pregnancy ^e		
S-albumin	S-sodium	S-human chorionic		
B-glucose (fasting)	S-potassium	gonadotropin		
	S-calcium (total)			
B - blood: S - serum: U - urine				

a. Haematology at Screening, Day -1, Day 14, and Day 28.

b. Clinical chemistry at Screening, Day -1, Day 14, and Day 28. Exception: Lipids - done only at Screening and Day 28/End of Study.

There were no apparent trends or clinically significant abnormalities in the mean safety laboratory tests overall or within CLB treatments or trends in individual subjects' values.

7.4.3 Vital Signs

There were no apparent trends or clinically significant abnormalities in the vital signs determinations.

7.4.4 Electrocardiograms (ECGs)

A standard EKG was performed during the screening period and on Day -1 to confirm eligibility. The EKG was repeated on Days 1 and 15 at both 0 hour (predose) and post dose at 2 and 24 hours. A final EKG was done on day 28 (end of study).

None of the EKG findings were considered clinically significant by the investigator.

7.4.5 Special Safety Studies/Clinical Trials

An assessment of suicidal ideation and behavior, the C-SSRS, was administered by interview at Day -1 and on days 6, 14, 20, and 28 (end of study).

None of the subjects had any suicidal ideation or behavior at any time point based on assessments with the C-SSRS questionnaires.

7.4.6 Immunogenicity

See Section 7.2

7.5 Other Safety Explorations

See Section 7.2

7.6 Additional Safety Evaluations

See Section 7.2

7.7 Additional Submissions / Safety Issues

None

Reviewer Note:

No differences in safety and tolerability were observed between single doses of 20 mg clobazam tablets (approved under NDA 202067) and clobazam oral suspension.

No deaths, serious adverse effects, or significant adverse effects were reported and all subjects completed the study. There were no findings of clinical concern in vital signs, physical and neurological exams, clinical laboratory findings, EKG, or C-SSRS (suicidality) data.

There was no difference in the incidence of the adverse effects observed between clobazam tablets and clobazam oral suspension, and all are already described in current labeling for the clobazam tablet.

8 Postmarket Experience

Clobazam is a 1, 5–benzodiazepine approved for the treatment of anxiety disorders, epilepsy, and similar indications in over 80 countries worldwide.

In Periodic Safety Update Reports submitted to the European Medicines Agency by Aventis from November 1994 to February 2010, there were over 3.4 million patient years of exposure.

Updated safety reports since Oct 2011 approval of tablets have not revealed any new adverse events requiring revised labeling.

9 Appendices

9.1 Literature Review/References

None.

9.2 Labeling Recommendations

The labeling will be essentially unchanged from approved labeling of October 2011 except for the addition of oral suspension as an alternative dosing form and addition of dosing instructions for the oral suspension.

9.3 Advisory Committee Meeting

None required.

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/s/

PHILIP H SHERIDAN 12/12/2012

NORMAN HERSHKOWITZ 12/12/2012