

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203993Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	203993	Brand Name	Onfi™
OCP Division (I, II, III, IV, V)	DCP-1	Generic Name	Clobazam
Medical Division	HFD-120	Drug Class	Anticonvulsant
OCP Reviewer	Ta-Chen Wu, Ph.D.	Indication(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ≥ 2 years of age
OCP Team Leader	Angela Yuxin Men, M.D., Ph.D.	Dosage Form	Suspension: 2.5 mg/mL
Pharmacometrics Reviewer	None	Dosing Regimen	ONFI should be administered in divided doses twice daily, dosed according to body weight (the 5 mg dose can be administered as a single daily dose). <u>≤ 30 kg Body Weight:</u> <ul style="list-style-type: none"> • Starting dose: 5 mg • Starting Day 7: 10 mg • Starting Day 14: 20 mg <u>> 30 kg Body Weight:</u> <ul style="list-style-type: none"> • Starting dose: 10 mg • Starting Day 7: 20 mg • Starting Day 14: 40 mg
Pharmacogenomics Reviewer	None		
Date of Submission	02/28/2012	Route of Administration	Oral
Estimated Due Date of OCP Review	10/15/2012	Sponsor	Lundbeck ILC
Medical Division Due Date	10/29/2012	Priority Classification	S
PDUFA Due Date	12/28/2012		

Clin. Pharm. and Biopharm. Information

Summary:

ONFI (clobazam) Tablets (5, 10, and 20 mg strengths) were approved on 21 October 2011 (NDA 202067) in the US for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS). The applicant seeks approval for a new oral suspension formulation targeted for LGS patients who have difficulty swallowing tablets.

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The current NDA submission contains a relative bioavailability (BA) study (Study 14033A) comparing an oral suspension formulation (2.5 mg/mL) to the approved 20 mg tablet to support the approval. In addition, the applicant provides a statistical analysis of in-vitro binding data for clobazam and N-desmethyloclobazam (Study 176-808-2012) to support a more robust Mechanism of Action statement in the included proposed labeling. No study was conducted by the Applicant to evaluate the potential food effect on BA of oral suspension.

Clinical pharmacology development program

Type of Study	Study Identifier	Objectives(s) of the Study	Study Design & Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Exposed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
BA	14033A	Assess the relative bioavailability, safety, and tolerability of a single 20 mg oral dose of clobazam (CLB) administered as a suspension as compared to a CLB 20 mg oral tablet	Open label, randomized, single-dose, 2 way crossover	Oral CLB tablet: 20 mg Oral CLB suspension: 20 mg	CLB 20 mg tablet: 30 CLB 20 mg suspension: 30	Healthy subjects	Two single doses separated by a 14 day drug free period

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Sponsor provided Word and PDF version, both clean and with track-changes, for the proposed labeling
Reference Bioanalytical and Analytical Methods	X			A validated LC/MS/MS method: Validation: Report 14210 Individual study: Report 14200
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			Study 14033A (Tablets as reference), conducted under fasted condition
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				No food-effect study was conducted.
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Request for ped waiver in neonates (birth to 1 month of age) and infants (1 month up to 2 years of age)
Literature References	X			7
Total Number of Studies	2	2	2	Study 14033A + Validation report

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			N/A	Only 1 relative BA study with TBM formulation

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

2	Has the applicant provided metabolism and drug-drug interaction information?			N/A	Labeling information
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	Yes			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	Yes			
5	Has a rationale for dose selection been submitted?	Yes			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	Yes			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	Yes			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	Yes			Bioanalytical report provided separately without hyperlinking from the study report
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			N/A	No prior pre-submission discussions occurred for this application
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			N/A	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	Yes			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			N/A	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			N/A	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			N/A	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			N/A	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			N/A	
17	Is there adequate information on the	Yes			

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	pharmacokinetics and exposure-response in the clinical pharmacology section of the label?				
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	(Yes)			Effect of food will need to be evaluated for the new formulation so it can be taken without regard to food like the approved Tablets
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		No		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- We noticed that effect of food has not been evaluated for the proposed new formulation. Given the labeling recommendation for the oral tablets, please address how oral suspension will be administered with regard to food intake.
- Please provide a “definition” file in PDF format for the electronic datasets for Study 14033A.

We request a DSI inspection of the clinical and the analytical sites for the following study (Study 14033A (relative bioavailability study)):

Clinical site: SeaView Research, Miami, U.S.A. (Investigator: Axel Juan, MD)

Analytical site: Non-Clinical Safety Research, Department of Bioanalysis, H. Lundbeck A/S, (b) (4)

Ta-Chen Wu

Reviewing Clinical Pharmacologist

Date

Angela Yuxin Men

Team Leader/Supervisor

Date

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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/

TA-CHEN WU
12/10/2012

YUXIN MEN
12/10/2012

CLINICAL PHARMACOLOGY REVIEW

NDA:	203993
Brand Name:	ONFI™
Generic Name:	Clobazam
Dosage Form & Strength:	Oral Suspension (2.5 mg/mL)
Indication:	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients ≥2 years of age
Applicant:	Lundbeck Inc.
Submission:	505(b)(1), Standard
Submission Dates:	02/28/2012, 05/24/2012
OND Division:	OND-1/Division of Neurology Drug Products
OCP Divisions:	Clinical Pharmacology DCP-1
Primary Reviewer:	Ta-Chen Wu, Ph.D.
Team Leader:	Angela Yuxin Men, M.D., Ph.D.

Table of Contents

1.	Executive Summary	2
1.1	Recommendation	2
1.2	Phase IV Commitment	2
1.3	Summary of Important Clinical Pharmacology and Biopharmaceutics Findings ..	2
2.	Question Based Review	4
2.1	General Attributes	4
2.2	General Clinical Pharmacology	5
2.3	Intrinsic Factors	6
2.4	Intrinsic Factors	6
2.5	General Biopharmaceutics	6
2.6	Analytical Section	10
3.	Detailed Labeling Recommendations	11
4.	Appendices	11
4.1	Proposed Labeling	11
4.2	Individual Study Review	19
4.3	OCP Filing/Review Form	23

1. Executive Summary

Onfi[®] (clobazam) Tablets of 5-, 10-, and 20-mg strengths were approved on October 21, 2011 for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients aged 2 years and older (NDA 202067). The sponsor is seeking approval of Onfi[™] (clobazam) Oral Suspension as an adjunctive therapy for the same indication for patients who have difficulty swallowing tablets.

To support the approval of this application, the Sponsor conducted a single-dose relative bioavailability study to demonstrate the bioequivalence between the proposed Onfi[™] oral suspension and the current marketed tablets (20-mg strength). Information pertaining to Clinical pharmacology and biopharmaceutics will be cross-referenced to the approved Onfi[®] tablets. No new clinical efficacy studies were conducted.

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 1 (OCP/DCP-1) has reviewed the submission and finds NDA 203993 acceptable from an OCP perspective provided that an agreement is reached between the Sponsor and the Agency regarding the revised labeling language.

1.2 Phase IV Commitment

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics:

After single dose administration of the oral suspension under fasted conditions, the median T_{max} was approximately 0.75 hour (ranging 0.5~2 hours), indicating a faster absorption compared to oral tablet (T_{max} ~2 hours). Similar pharmacokinetic profiles of clobazam and N-CLB were observed between oral suspension and tablet. The mean elimination half-lives of clobazam were similar between oral suspension (39.7 hours) and tablet (38.8 hours) (see Section 2.2.2 for additional pharmacokinetic information). Oral tablets and suspension were shown to have similar bioavailability under fasted condition based on clobazam exposure (C_{max} and AUC).

PK Comparison of Oral Suspension and Reference Tablet Formulations:

The point estimates and corresponding 90% CIs for the geometric mean ratios for the exposure measures (AUC_{0-inf} and AUC_{0-t}) between CLB oral suspension and oral tablets were within the BE acceptance criteria of 0.8-1.25. For C_{max}, the oral suspension was approximately 19% higher than that from oral tablet, whereas the upper bound of the 90% CI (i.e., 1.27) fell slightly outside of the upper limit of the acceptance BE criteria.

However, this difference is not considered clinically significant. Results from this relative bioavailability study showed that clobazam oral suspension and reference clobazam oral tablets are bioequivalent.

Food Effect:

The food effect on Onfi™ oral suspension has not been studied. Upon the OCP request, the Sponsor provided justifications for not needing a food effect study and for not anticipating a significant food effects to warrant any food restriction for dose administration and pertinent labeling languages for the suspension formulation.

From a clinical pharmacology perspective, in general, a food effect study is needed for the new formulation, such as Onfi™ oral suspension, as we cannot completely rule out the potential food-effect and determine the extent of such effect, if it occurs, without a study. A potential reduction of clobazam systemic exposure carried a clinical concern during the review cycle. However, upon a thorough review of the justifications and the scientific reasoning for the particular case of clobazam, we concluded that a positive or an insignificant food effect, rather than a clinically significant negative effect, is more likely to occur for the Onfi™ oral suspension. Therefore, no food restriction and pertinent labeling languages are recommended (see Section 2.5.3 for details).

Ta-Chen Wu, Ph.D.
Reviewer, Neurology Drug Products,
DCP-1, Office of Clinical Pharmacology

Concurrence: Angela Men, M.D., Ph.D.
Team Leader, Neurology Drug Products
Office of Clinical Pharmacology

cc: HFD-120 NDA 203993
CSO/SL Sun
HFD-860 /DDD DCP-1/R. Upoor
/DD DCP-1/M. Mehta

2. Question Based Review

2.1 General Attributes

2.1.1 What are therapeutic indication(s) and the proposed mechanisms of action of Onfi?

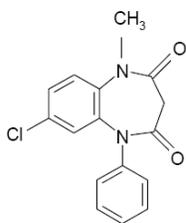
Onfi™ (clobazam) oral suspension is proposed as an adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ≥ 2 years of age.

The exact mechanism of action of clobazam (CLB), a 1,5-benzodiazepine, and its active metabolite, N-desmethylclobazam (N-CLB), is not fully understood. However, it is thought to involve potentiation of GABAergic neurotransmission from binding at the GABAA receptor benzodiazepine site. Both clobazam and N-CLB have in vitro binding affinities for the $\alpha 2$ subunit of the GABAA receptor that are significantly greater than their affinities for the $\alpha 1$ and $\alpha 3$ subunits.

2.1.2 What are the highlights of physico-chemical properties of the drug substance?

Clobazam, the active ingredient of Onfi™, is chemically known as 7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4-(3H,5H)-dione, without chiral centers in the structure. Its molecular formula is $C_{16}H_{13}ClN_2O_2$ and the molecular weight is 300.7. Clobazam is a white or almost white, crystalline powder that is slightly soluble in water, freely soluble in methylene chloride, and sparingly soluble in ethanol. The pH value for an aqueous solution is in the range of 5.5-7.5. The structure for clobazam drug substance is provided in the figure below.

Figure 1. Chemical structure of clobazam



2.1.3 What are the proposed dosage(s) and route(s) of administration?

The total daily dose of clobazam suspension should be administered orally at the following proposed dosing regimens according to body weight, as shown in the table below (refer to the approved Onfi® tablet label). Onfi™ should be administered in divided doses twice daily, dosed according to body weight (the 5 mg dose can be administered as a single daily dose). Oral suspension should be well shaken before the administration with syringe.

Table 1. Recommended total daily dosing by weight group (Onfi® tablet label)

	≤ 30 kg Body Weight	> 30 kg Body Weight
--	--------------------------	-----------------------

Starting Dose	5 mg	10 mg
Starting Day 7	10 mg	20 mg
Starting Day 14	20 mg	40 mg

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

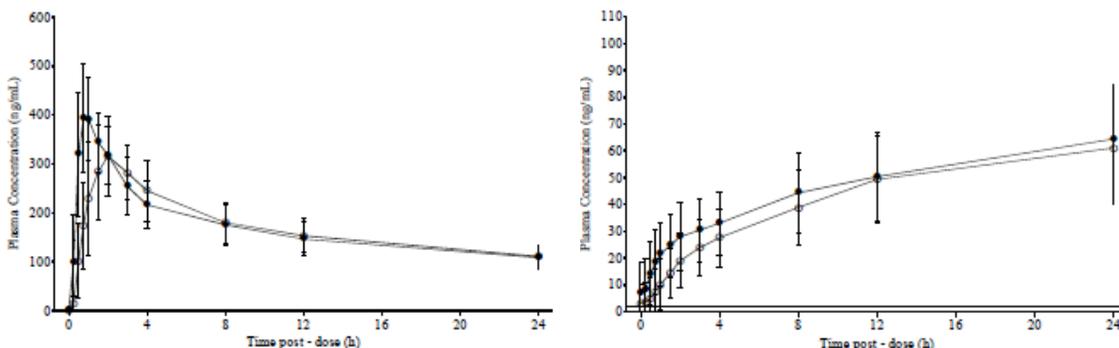
To support the approval of the application, the Sponsor conducted a single-dose relative bioavailability study (Study 14033A) to demonstrate the bioequivalence between the proposed Onfi™ oral suspension and the current marketed tablets of the same 20-mg strength. Information pertaining to Clinical pharmacology and biopharmaceutics, as well as dosage administration, will be cross-referenced to the approved Onfi® label. No new clinical efficacy studies were conducted.

Also included in the current submission are results from a non-clinical study (Study 176-808-2012) to support a more robust mechanism of action statement in the proposed labeling.

2.2.2 What are the PK characteristics of the drug and its major metabolite?

The pharmacokinetics of clobazam and N-CLB was evaluated in a single dose bioavailability study (Study 14033A) comparing the approved tablet dosage form (20 mg strength) and the proposed oral suspension dosage form (8 mL x 2.5 mg/mL). The mean (SD) plasma concentration-time profiles of clobazam and N-CLB following single-doses of clobazam oral suspension and tablet are presented in the Figure 2 below. Summary of key pharmacokinetic parameters is provided in the table below and detailed in Section 4.2 Individual Study Review. Detailed information pertinent to absorption, distribution, metabolism and elimination is available in the approved label for Onfi® Tablets.

Figure 2. Mean (SD) plasma concentration-time profiles of clobazam (Left) and N-CLB (Right) following single-doses of clobazam oral suspension and tablet



● Treatment A: 20 mg CLB suspension; ○ Treatment B: 20 mg CLB tablet.

The observed pharmacokinetic properties are consistent in general with those reported for clobazam tablets (refer to the approved Onfi[®] labeling for details describing absorption, distribution, metabolism and elimination in). Of note, absorption of clobazam from oral suspension was faster than tablet, with corresponding shortened Tmax at approximately 0.75 hour compared to 2 hours for oral tablets.

Table 2. Summary of single-dose pharmacokinetic parameters (Mean (SD)) for clobazam and N-CLB following administration of oral suspension and tablet formulations (Study 14033A)

Treatment		Cmax (ng/mL)	Tmax (hr) ^a	AUC0-t (hr·ng/mL)	AUC0-inf (hr·ng/mL)	t _{1/2} (hr)
Test: CLB 20-mg Suspension	CLB	421 (86.1)	0.75 (0.50-2.00)	10007 (2806)	10227 (2897)	39.7 (14.9)
	N-CLB	79.6 (24.5)	48.0 (36.0-120.0)	12085 (4803)	13087 (6175)	59.5 (23.1)
Reference: CLB 20-mg Tablet	CLB	354 (71.4)	2.00 (1.00-4.00)	10032 (2732)	10261 (2781)	38.9 (13.8)
	N-CLB	79.4 (25.0)	48.0 (12.0-120.0)	12822 (5218)	14668 (7466)	72.3 (34.3)

a. Median (range) for Tmax

2.2.3 What is the inter- and intra-subject variability of PK parameters in healthy subjects and patients?

The inter-subject variability of clobazam is considered to be moderate. The mean inter-subject variability of key pharmacokinetic parameters for clobazam and N-CLB in Study 14033A in healthy subjects was 20-30% and 30-50%, respectively, similar to that observed for the Onfi[®] tablets.

2.3 Intrinsic Factors

Not applicable

2.4 Extrinsic Factors

Not applicable

2.5 General Biopharmaceutics

2.5.1 What are the compositions of the proposed Onfi Oral Suspension?

Clobazam oral suspension is an off-white berry flavored liquid containing clobazam at a concentration of 2.5 mg/mL.

Table 3. Constituents of the suspension formulation used in Study 14033A

Component	Quantity per mL	Function	Quality Standard
Clobazam (b) (4)	2.50 mg	Drug Substance	EP
Magnesium Aluminum Silicate (b) (4)			(b) (4)
Xanthan gum			
Citric Acid Monohydrate			
Disodium Hydrogen Phosphate Dihydrate			
Simethicone Emulsion (b) (4)			
Polysorbate 80			
Methylparaben			
Propylparaben			
Propylene Glycol			
Sucralose			
Maltitol Solution			
Berry flavor			
Citric Acid Monohydrate (b) (4)			
Disodium Hydrogen Phosphate Dihydrate (b) (4)			
Purified Water (b) (4)			

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation?

A formal BCS classification for clobazam has not been determined.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The oral suspension formulation used in the relative bioavailability study (Study 14033A) is the same as the proposed commercial formulation. Therefore, no study is necessary for bridging the formulations.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the reference drug product?

Study 14033A was a single dose, single center, open-label, randomized, two-way crossover study conducted under fasted conditions to evaluate the bioavailability of clobazam administered as an oral 20 mg clobazam suspension (Test) and as a single 20 mg tablet (Reference) in a 30 healthy adult men and women.

The suspension formulation was bioequivalent to the tablet formulation in terms of total exposure (AUC_{0-t} and AUC_{0-inf}), and the 90% CI for the ratios of AUCs were both contained within the 0.80 to 1.25 range. The C_{max} of clobazam was higher with the suspension than the tablet by 19% with corresponding shorter T_{max}, whereas the upper bound of the 90% CI being 1.27, slightly exceeding the upper limit (1.25) of the acceptance BE criteria. The observed differences in C_{max} were not considered clinically significant.

Table 4. Summary of the statistical analysis for clobazam pharmacokinetic parameters (Study 14033A)

Pharmacokinetic Parameter	CLB Suspension (Treatment A) (N=30) ^a	CLB Tablet (Treatment B) (N=30) ^a	Geometric Mean Ratio [90% CI] ^b
AUC _{0-inf} (ng•h/mL)	9833	9885	0.995 [0.976, 1.01]
AUC _{0-t} (ng•h/mL)	9626	9659	0.997 [0.977, 1.02]
C _{max} (ng/mL)	414	347	1.19 [1.12, 1.27]

a. All data presented as Geometric LSM, except for T_{max} (median (min, max))

b. Based on geometric means

2.5.3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The food effect on Onfi™ oral suspension has not been studied.

The Office of Clinical Pharmacology sent an Information Request to the Sponsor (dated May 09, 2012 as part of the filing communication) concerning a lack of study for effect of food, and hence the implication for dose administration, as presented as follows:

“We noticed that the effect of food has not been evaluated for the proposed new formulation. Given the labeling recommendation for the oral tablets to be taken without regard to food, you need to address how the oral suspension can also be administered under the fed condition.”

The Sponsor’s response (dated May 24, 2012) is summarized as follows:

- Near complete absorption: ≥82% and 11% of the radioactivity administered were recovered in urine and feces, respectively, in a mass-balance study (NDA 202067)
- BE was established between oral tablet and oral solution (NDA 202067)
- High-fat food had clinically insignificant effect on clobazam absorption from oral tablet (AUC↔, C_{max}↓ by 22%, T_{max}↑ by 1 hr; NDA 202067)
- Clobazam tablets had rapid disintegration and dissolution rate (i.e., > (b) (4) dissolution in 45 min; NDA 202067). Same clobazam drug substance (b) (4) was used in tablet and oral suspension formulations and, therefore, the suspension formulation would be expected to behave similarly in the presence of food.
- All excipients in the oral suspension are commonly used materials (see Section 2.5.1) and food is unlikely to affect absorption of clobazam from the suspension.
- BE was established between oral tablet and oral suspension based on exposure (AUCs). However, the oral suspension had a faster rate of oral absorption resulting in attainment of earlier T_{max} (0.75 vs. 2.00 hours) and higher C_{max} (19%) values compared to the tablets (current NDA submission).
- Given the above physicochemical and pharmacokinetic characteristics of clobazam, food effect with the suspension formulation would be the same as that with the tablet, and therefore, there is no need to conduct a food effect study with the oral suspension.

In a communication with ONDQA review team (August 01, 2012), Dr. Akm Khairuzzaman indicated as follows:

“Food effect: Although applicant has conducted a food effect BA study in their previous NDA-202067 (Clobazam Tablets, which showed no significant food effect), no food effect study was found under this NDA for this new formulations (suspension). A suspension preparation generally instantly deliver all the active drug substance from the product compared to its immediate release tablets, whereby the active drug substance generally exists in the form of a granule. Between the clobazam tablets and the suspension preparation there could be following differences that may lead to differences in food effect:

- i. API particle size differences*
- ii. Dissolution differences*
- iii. Inactive ingredient such as surfactant present in clobazam suspension may influence dissolution/solubilization differently in fed condition*

As per the “Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies”, important food effect on BA are least likely to occur with BCS class I types of drug, which does not apply to clobazam. Therefore in this case, the relative direction and magnitude of food effects on this new formulation (suspension) BA and the effect on the demonstration of BE are difficult to predict without the presence of a fed BE study. Applicant should either conduct a fed BE study in order to resolve this issue or can address this issue by appropriate instruction in the labeling.”

Reviewer’s comments:

The food intake can change stomach pH, increase the bile micelle concentration and binding, delay gastric emptying time, increase the fluid volume, increase splanchnic blood flow, and interact with the dosage form or the drug substance. For these reasons from a regulatory standpoint we typically require a food-effect study for the proposed new oral formulations to examine the potential food-effect and the extent of such effect. Considering the aforementioned differences between the oral tablet and suspension formulations, an interaction of food with the Onfi™ oral suspension cannot be excluded. Given the extensive gastrointestinal absorption of clobazam, we are more concerned about a potential decrease in clobazam AUC under fed conditions (see 2nd and 3rd bullet points below). Depending on the magnitude of the reduction in clobazam exposure if it should occur, this effect could be of clinical concern. In the absence of a food-effect study for the Onfi™ oral suspension, we reviewed the following justifications and literature information:

- Pertinent information include the extent of clobazam gastrointestinal absorption, the bioequivalence between single-dose Onfi tablet and oral suspension under fasted conditions, a lack of significant food effect on the approved tablet formulation, and a relatively wide therapeutic window for clobazam.
- It is noted that an excipient polysorbate 80 (b) (4) is used in oral suspension formulation but not in tablet formulation. In a publication [*European Journal of Pharmaceutical Sciences. 19:299-304 (2003)*], courtesy of Dr. Khairuzzaman, the authors Odeberg et al. reported an excipient (polysorbate 80)-drug interaction under fed conditions that polysorbate 80 enhanced bioavailability of lipophilic astaxanthin (as antioxidant with low BA) administered within 15 minutes after breakfast.

However, the effect of polysorbate 80 in fasted conditions was not studied in this publication. Considering the high extent of gastrointestinal absorption of clobazam (refer to the NDA 202067 review and the approved labeling for Onfi[®] tablets), if an absorption-enhancing effect (a positive food effect) by polysorbate 80 under fed conditions ever occurs, the increased systemic exposure of clobazam from the oral suspension would be considered clinically insignificant.

- Clobazam, a lipophilic compound, has high permeability and low solubility, and thus, more likely belongs to biopharmaceutical classification system (BCS) Class II categorization based on its physical-chemical properties and the known study results in humans (NDA 202067 for Onfi[®] tablets). It has been reported in literature that food effects on the extent of absorption (or bioavailability) can generally be predicted based on BCS categorization, with BCS Class II drugs showing a tendency of positive food effects [*Wu CY and Benet LZ. Pharm Res 22(1): 11-23 (2005)*]. The potential negative food effect was projected for drugs in the Class III categorization to which clobazam is unlikely to belong. Clobazam has a reported pKa value of 6.65 and pH range of 5.5~7.5. Therefore, the net effect of food would largely hinge on the balance between the respective changes in permeability and in solubility by the micelle concentration, as reported for the Class II drugs [*Sugano et al. Eu J Pharm Sci 40:118-124 (2010)*; *Kawai et al. Drug Metab. Pharmacokinet 26(2):180-191 (2011)*]. As reported in these publications, for the solubility-limited cases, a positive food effect and a lack of food effect were anticipated for epithelial membrane limited case and unstirred water layer (UWL)-limited case, respectively. A negative food effect, on the other hand, is anticipated for permeability-limited scenario which clearly is not the case for clobazam.

In conclusion, although potential reduction of clobazam systemic exposure carried a clinical concern during the review cycle, upon a thorough review of the justifications and the scientific reasoning for clobazam, we conclude that a positive or an insignificant food effect, rather than a clinically significant negative effect, is more likely to occur for the Onfi[™] oral suspension. As discussed above, an increase in systemic exposure of clobazam from the oral suspension in the presence of food would not be considered clinically significant. Therefore, no food restriction and pertinent labeling language are recommended. Onfi[™] oral suspension can be taken with or without food.

2.6 Analytical Section

2.6.1 Were the active moieties identified and measured in the plasma in the clinical pharmacology study?

Yes. Both the parent compound and an active metabolite were measured in all studies.

2.6.2 What analytical method was used to determine drug concentrations and was the analytical assay method adequately validated?

A validated LC/MS/MS method was used to simultaneously quantitate clobazam and N-CLB in plasma. The bioanalytical assay for the concomitant analysis of clobazam and N-

CLB is based on protein precipitation and analysis of the supernatant by LC/MS/MS. The calibration and QC samples were prepared in blank human plasma. The standard curves are linear in the 2.00~200 ng/mL range for clobazam and the 1.00~100 ng/mL range for N-CLB. Summary of bioanalytical assay for clobazam and N-CLB is provided in the table below.

Further, the bioanalytical methods for in-study performance were found acceptable. Following the Agency’s OSI inspection, no objectionable conditions were observed and no Form FDA 483 was issued. It was recommended that the clinical and bioanalytical portions of study 14033A be accepted for review.

Table 5. Bioanalytical summary for clobazam and N-CLB (Study Report 14210):

Parameter	Clobazam	N-CLB
Method	LC/MS/MS	LC/MS/MS
LLOQ	2.00 ng/mL	1.00 ng/mL
Linear range	2.00-200 ng/mL	1.00-150 ng/mL
QC samples	6.00, 20.0, 160	3.00, 10.00, 80.0
Accuracy	89.3% - 108.0%	89.5% - 105%
Precision	3.1% - 5.3%	5.2% - 7.5%
Freeze-thaw stability	3 cycles; Precision = 1.2 - 1.4% Accuracy = 94.7 - 96.8%	3 cycles; Precision = 1.3 – 2.0% Accuracy = 93.3 - 94.5%

3. Detailed Labeling Recommendations

The Office of Clinical Pharmacology has reviewed the proposed labeling for Onfi™ (clobazam) oral suspension and found it acceptable provided that the recommended revisions are made to the labeling language (see Section 4.1 Proposed Labeling).

4. Appendices

4.1 Proposed Labeling

The following working version of the labeling describes the clinical pharmacology-related sections that were agreed upon between the Agency and the Sponsor.

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

2.3 Important Administration Instructions

ONFI Tablet Oral Administration

ONFI tablets can be taken with or without food.

ONFI tablets can be administered either whole or crushed and mixed in applesauce.

ONFI Oral Suspension Oral Administration

ONFI oral suspension can be taken with or without food [see *Clinical Pharmacology* (12.3)].

2.4 Dosage Adjustments in Geriatric Patients

Plasma concentrations at any given dose are generally higher in the elderly: proceed slowly with dose escalation. The starting dose should be 5 mg/day for all elderly patients. Then titrate elderly patients according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on weight) may be started on day 21 [see *Use in Specific Populations* (8.5)].

2.5 Dosage Adjustments in CYP2C19 Poor Metabolizers

In CYP2C19 poor metabolizers, levels of N-desmethylclobazam, clobazam's active metabolite, will be increased. Therefore, in patients known to be CYP2C19 poor metabolizers, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group) may be started on day 21 [see *Use in Specific Populations* (8.6), *Clinical Pharmacology* (12.5)].

2.6 Patients with Renal Impairment

No dose adjustment is required for patients with mild and moderate renal impairment. There is no experience with ONFI in patients with severe renal impairment or end stage renal disease (ESRD). It is not known if clobazam or its active metabolite, N-desmethylclobazam, is dialyzable [see *Use in Specific Populations* (8.7), *Clinical Pharmacology* (12.3)].

2.7 Dosage Adjustments in Patients with Hepatic Impairment

ONFI is hepatically metabolized; however, there are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of ONFI. For this reason, proceed slowly with dosing escalations. For patients with mild to moderate hepatic impairment (Child-Pugh score 5-9), the starting dose should be 5 mg/day in both weight groups. Then titrate patients according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, start an additional titration on day 21 to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group). There is inadequate information about metabolism of ONFI in patients with severe hepatic impairment. Therefore no dosing recommendation in those patients can be given [see *Use in Specific Populations (8.8), Clinical Pharmacology (12.3)*].

7 DRUG INTERACTIONS

7.1 Effect of ONFI on Other Drugs

Hormonal Contraceptives

ONFI is a weak CYP3A4 inducer. As some hormonal contraceptives are metabolized by CYP3A4, their effectiveness may be diminished when given with ONFI. Additional non-hormonal forms of contraception are recommended when using ONFI [see *Clinical Pharmacology (12.3), Patient Counseling Information (17)*].

Drugs Metabolized by CYP2D6

ONFI inhibits CYP2D6. Dose adjustment of drugs metabolized by CYP2D6 may be necessary [see *Clinical Pharmacology (12.3)*].

7.2 Effect of Other Drugs on ONFI

Strong and moderate inhibitors of CYP2C19

Strong and moderate inhibitors of CYP2C19 may result in increased exposure to N-desmethylclobazam, the active metabolite of clobazam. This may increase the risk of dose-related adverse reactions. Dosage adjustment of ONFI may be necessary when coadministered with strong CYP2C19 inhibitors (e.g., fluconazole, fluvoxamine, ticlopidine) or moderate CYP2C19 inhibitors (e.g., omeprazole) [see *Clinical Pharmacology (12.3)*].

7.3 CNS Depressants and Alcohol

Concomitant use of ONFI with other CNS depressants may increase the risk of sedation and somnolence [see *Warnings and Precautions (5.2)*].

Alcohol, as a CNS depressant, will interact with ONFI in a similar way and also increases clobazam's maximum plasma exposure by approximately 50%. Therefore, caution patients or their caregivers against simultaneous use with other CNS depressant drugs or alcohol, and cautioned that the effects of other CNS

depressant drugs or alcohol may be potentiated. [see *Warnings and Precautions (5.2)*].

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

Clinical studies of ONFI did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, elderly subjects appear to eliminate clobazam more slowly than younger subjects based on population pharmacokinetic analysis. For these reasons, the initial dose in elderly patients should be 5 mg/day. Patients should be titrated initially to 10-20 mg/day. Patients may be titrated further to a maximum daily dose of 40 mg if tolerated [see *Dosage and Administration (2.2)*, *Clinical Pharmacology (12.3)*].

8.6 CYP2C19 Poor Metabolizers

Concentrations of clobazam's active metabolite, N-desmethyloclobazam, are higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this reason, dosage modification is recommended [see *Dosage and Administration (2.3)*, *Clinical Pharmacology (12.5)*].

8.7 Renal Impairment

The pharmacokinetics of ONFI were evaluated in patients with mild and moderate renal impairment. There were no significant differences in systemic exposure (AUC and C_{max}) between patients with mild or moderate renal impairment and healthy subjects. No dose adjustment is required for patients with mild and moderate renal impairment. There is essentially no experience with ONFI in patients with severe renal impairment or ESRD. It is not known if clobazam or its active metabolite, N-desmethyloclobazam, is dialyzable [see *Dosage and Administration (2.4)*, *Clinical Pharmacology (12.3)*].

8.8 Hepatic Impairment

ONFI is hepatically metabolized; however, there are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of ONFI. For this reason, dosage adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh score 5-9). There is inadequate information about metabolism of ONFI in patients with severe hepatic impairment. [see *Dosage and Administration (2.5)*, *Clinical Pharmacology (12.3)*].

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

The peak plasma levels (C_{max}) and the area under the curve (AUC) of clobazam are dose-proportional over the dose range of 10-80 mg following single- or

multiple-dose administration of ONFI. Based on a population pharmacokinetic analysis, the pharmacokinetics of clobazam are linear from 5-160 mg/day. Clobazam is converted to N-desmethyclobazam which has about 1/5 the activity of clobazam. The estimated mean elimination half-lives ($t_{1/2}$) of clobazam and N-desmethyclobazam were 36-42 hours and 71-82 hours, respectively.

Absorption

Clobazam is rapidly and extensively absorbed following oral administration. The time to peak concentrations (T_{max}) of clobazam tablets under fasted conditions ranged from 0.5 to 4 hours after single- or multiple-dose administrations. The relative bioavailability of clobazam tablets compared to an oral solution is approximately 100%. After single dose administration of the oral suspension under fasted conditions, the T_{max} ranged from 0.5 to 2 hours. Based on exposure (C_{max} and AUC) of clobazam, ONFI tablets and suspension were shown to have similar bioavailability under fasted condition. The administration of ONFI tablets with food or when crushed in applesauce does not affect absorption. Although not studied, the oral bioavailability of the oral suspension is unlikely to be affected under fed conditions.

Distribution

Clobazam is lipophilic and distributes rapidly throughout the body. The apparent volume of distribution at steady state was approximately 100 L. The *in vitro* plasma protein binding of clobazam and N-desmethyclobazam is approximately 80-90% and 70%, respectively.

Metabolism and Excretion

Clobazam is extensively metabolized in the liver, with approximately 2% of the dose recovered in urine and 1% in feces as unchanged drug. The major metabolic pathway of clobazam involves N-demethylation, primarily by CYP3A4 and to a lesser extent by CYP2C19 and CYP2B6. N-desmethyclobazam, an active metabolite, is the major circulating metabolite in humans, and at therapeutic doses, plasma concentrations are 3-5 times higher than those of the parent compound. Based on animal and *in vitro* receptor binding data, estimates of the relative potency of N-desmethyclobazam compared to parent compound range from 1/5 to equal potency. N-desmethyclobazam is extensively metabolized, mainly by CYP2C19. N-desmethyclobazam and its metabolites comprise ~94% of the total drug-related components in urine. Following a single oral dose of radiolabeled drug, approximately 11% of the dose was excreted in the feces and approximately 82% was excreted in the urine.

The polymorphic CYP2C19 is the major contributor to the metabolism of the pharmacologically active N-desmethyclobazam [see *Clinical Pharmacology* (12.5)]. In CYP2C19 poor metabolizers, levels of N-desmethyclobazam were 5-

fold higher in plasma and 2- to 3-fold higher in the urine than in CYP2C19 extensive metabolizers.

Pharmacokinetics in Specific Populations

Age

Population pharmacokinetic analyses showed that the clearance of clobazam is lower in elderly subjects compared to other age groups (ages 2 to 64). Dosing should be adjusted in the elderly [see *Dosage and Administration (2.2)*].

Sex

Population pharmacokinetic analyses showed no difference in the clearance of clobazam between women and men.

Race

Population pharmacokinetic analyses including Caucasian (75%), African American (15%), and Asian (9%) subjects showed that there is no evidence of clinically significant effect of race on the clearance of clobazam.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of clobazam was evaluated in patients with mild (creatinine clearance [CL_{CR}] > 50 to 80 mL/min; N=6) and moderate (CL_{CR} =30 to 50 mL/min; N=6) renal dysfunction, with matching healthy controls (N=6), following administration of multiple doses of ONFI 20 mg/day. There were insignificant changes in C_{max} (3-24%) and AUC ($\leq 13\%$) for clobazam or N-desmethyloclobazam in patients with mild or moderate renal impairment compared to patients with normal renal function. Patients with severe renal impairment or ESRD were not included in this study.

Hepatic Impairment

There are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of clobazam. In a small study, the pharmacokinetics of a 20 mg single oral dose of ONFI in 9 patients with liver impairment were compared to healthy controls (N=6). The C_{max} and the mean plasma clearance of clobazam, as well as the C_{max} of N-desmethyloclobazam, showed no significant change compared to the healthy controls. The AUC values of N-desmethyloclobazam in these patients were not available. Adjust dosage in patients with hepatic impairment [see *Dosage and Administration (2.5)*].

Drug Interaction Studies

In vitro studies:

Clobazam did not inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A4, UGT1A6, or UGT2B4 *in vitro*. N-desmethyloclobazam showed weak inhibition of CYP2C9, UGT1A4, UGT1A6 and UGT2B4.

Clobazam and N-desmethyloclobazam did not significantly increase CYP1A2 or CYP2C19 activities, but did induce CYP3A4 activity in a concentration-dependent manner. Clobazam and N-desmethyloclobazam also increased UGT1A1 mRNA but at concentrations much higher than therapeutic levels. The potential for clobazam or N-desmethyloclobazam to induce CYP2B6 and CYP2C8 has not been evaluated.

Clobazam and N-desmethyloclobazam do not inhibit P-glycoprotein (P-gp), but are P-gp substrates.

In vivo studies:

Potential for ONFI to Affect Other Drugs

The effect of repeated 40 mg once-daily doses of ONFI on the pharmacokinetic profiles of single-dose dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), caffeine (CYP1A2 substrate), and tolbutamide (CYP2C9 substrate), was studied when these probe substrates were given as a drug cocktail (N=18).

Clobazam increased AUC and C_{max} of dextromethorphan by 90% and 59%, respectively, reflecting its inhibition of CYP2D6 *in vivo*. Drugs metabolized by CYP2D6 may require dose adjustment when used with ONFI.

Clobazam decreased the AUC and C_{max} of midazolam by 27% and 24%, respectively, and increased the AUC and C_{max} of the metabolite 1-hydroxymidazolam by 4-fold and 2-fold, respectively. This level of induction does not call for dosage adjustment of drugs that are primarily metabolized by CYP3A4 when used concomitantly with ONFI. Some hormonal contraceptives are metabolized by CYP3A4 and their effectiveness may be diminished when given with ONFI. [see *Drug Interactions (7)*]. Repeated ONFI doses had no effect on caffeine and tolbutamide.

A population pharmacokinetic analysis indicated clobazam did not affect the exposure of valproic acid (a CYP2C9/2C19 substrate) or lamotrigine (a UGT substrate).

Potential for Other Drugs to Affect ONFI

Co-administration of ketoconazole (a strong CYP3A4 inhibitor) 400 mg once-daily for 5 days increased clobazam AUC by 54%, with an insignificant effect on

clobazam C_{max} . There was no significant change in AUC and C_{max} of N-desmethyloclobazam (N=18).

Strong (e.g., fluconazole, fluvoxamine, ticlopidine) and moderate (e.g., omeprazole) inhibitors of CYP2C19 may result in up to a 5-fold increase in exposure to N-desmethyloclobazam, the active metabolite of clobazam, based on extrapolation from pharmacogenomic data [see *Clinical Pharmacology (12.5)*]. Dosage adjustment of ONFI may be necessary when coadministered with strong or moderate CYP2C19 inhibitors [see *Drug Interactions (7)*].

The effects of concomitant antiepileptic drugs that are CYP3A4 inducers (phenobarbital, phenytoin, and carbamazepine), CYP2C9 inducers (valproic acid, phenobarbital, phenytoin, and carbamazepine), and CYP2C9 inhibitors (felbamate and oxcarbazepine) were evaluated using data from clinical trials. Results of population pharmacokinetic analysis show that these concomitant antiepileptic drugs did not significantly alter the pharmacokinetics of clobazam or N-desmethyloclobazam at steady-state.

Alcohol has been reported to increase the maximum plasma exposure of clobazam by approximately 50%. Alcohol may have additive CNS depressant effects when taken with ONFI [see *Warnings and Precautions (5.2)*, *Drug Interactions (7)*].

12.5 Pharmacogenomics

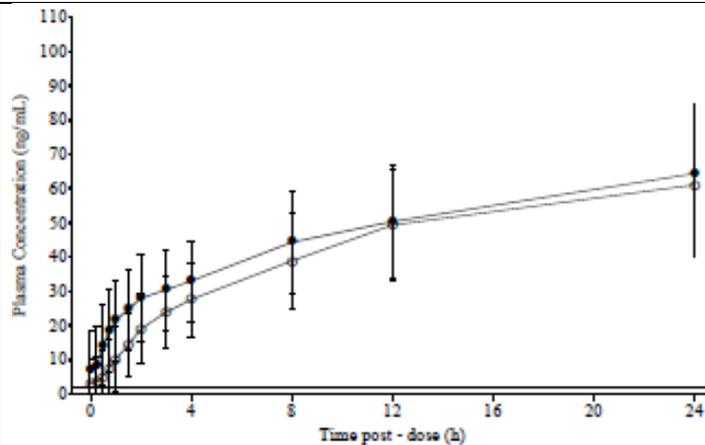
The polymorphic CYP2C19 is the main enzyme that metabolizes the pharmacologically active N-desmethyloclobazam. Compared to CYP2C19 extensive metabolizers, N-desmethyloclobazam AUC and C_{max} are approximately 3-5 times higher in poor metabolizers (e.g., subjects with $*2/*2$ genotype) and 2 times higher in intermediate metabolizers (e.g., subjects with $*1/*2$ genotype). The prevalence of CYP2C19 poor metabolism differs depending on racial/ethnic background. Dosage in patients who are known CYP2C19 poor metabolizers may need to be adjusted [see *Dosage and Administration (2.3)*].

The systemic exposure of clobazam is similar for both CYP2C19 poor and extensive metabolizers.

4.2 Individual Study Review

Study Report #	14033A																		
Title	Randomized, open-label, two-way crossover study investigating the relative bioavailability of Lu-00-638 (clobazam) oral suspension relative to oral tablets following a single 20 mg dose in healthy subjects																		
Investigator/Center	Axel Juan, MD/ SeaView Research, Miami, Florida, United States																		
Study Dates	July 25, 2011 ~ September 14, 2011																		
Objectives	Single-dose relative bioavailability, pharmacokinetics of CLB and N-CLB, safety and tolerability																		
Formulation	Treatment	Clobazam (CLB)	Batch number																
	A	Oral suspension (20 mg) - Test	P1437																
	B	Oral tablet (20 mg) - Reference	0804075																
Study Design	<ul style="list-style-type: none"> This was a single-center, randomized, open-label, 2-period, 2-way crossover study in healthy males and females, aged 18-45 years, inclusive. Doses were administered on Days 1 and 15, fasted, with 240 mL water and were separated by a washout period of 14 days before the crossover. <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>Treatment Sequence</th> <th>Dosing 1</th> <th>Dosing 2</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>A (Test)</td> <td>B (Reference)</td> </tr> <tr> <td>2</td> <td>B (Reference)</td> <td>A (Test)</td> </tr> </tbody> </table> <p>Test: CLB 20 mg (8 mL of 2.5 mg/mL) suspension Reference: CLB 20 mg tablet</p> <ul style="list-style-type: none"> Blood samples were collected up to 312 hours post-dose in both periods for drug concentration analysis of CLB and its major metabolite N-CLB. Safety and tolerability were assessed throughout the study (i.e., AEs, clinical safety laboratory tests, vital signs, weight, ECGs, physical examinations, and Columbia Suicide Severity Rating Scale (C-SSRSs)). Duration of study for each subject was 35 days. 			Treatment Sequence	Dosing 1	Dosing 2	1	A (Test)	B (Reference)	2	B (Reference)	A (Test)							
Treatment Sequence	Dosing 1	Dosing 2																	
1	A (Test)	B (Reference)																	
2	B (Reference)	A (Test)																	
PK Assessment	<p>For CLB and N-CLB:</p> <ul style="list-style-type: none"> Predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48, 72, 96, 120, 168, 216, 264, and 312 hours post-dose beginning on Days 1 and 15. <p>PK parameters: AUC_{0-t}, AUC_{0-inf}, AUC%_{extr}, C_{max}, CL/F (for CLB only), MRT, T_{max}, λ_z, V_z/F, and t_{1/2}</p>																		
Statistical Analysis	<ul style="list-style-type: none"> A mixed effect ANOVA model on log-transformed exposure measures. Point estimates and 90% CIs for geometric mean ratios of treatment differences (Test/Reference) for the log-transformed AUC_{0-inf}, AUC_{0-t}, and C_{max}, judged by BE acceptance criteria of 80-125%. 																		
Bioanalytical Methods	<p>Table. Assay performance</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="2"></th> <th>CLB (plasma)</th> <th>N-CLB (plasma)</th> </tr> </thead> <tbody> <tr> <td colspan="2">Method:</td> <td>HPLC/MS/MS</td> <td>HPLC/MS/MS</td> </tr> <tr> <td>Standard</td> <td>Range:</td> <td>2.00 – 200 ng/mL</td> <td>1.00 – 100 ng/mL</td> </tr> <tr> <td colspan="2">Curve:</td> <td>(6 points, not</td> <td>(6 points, not</td> </tr> </tbody> </table>					CLB (plasma)	N-CLB (plasma)	Method:		HPLC/MS/MS	HPLC/MS/MS	Standard	Range:	2.00 – 200 ng/mL	1.00 – 100 ng/mL	Curve:		(6 points, not	(6 points, not
		CLB (plasma)	N-CLB (plasma)																
Method:		HPLC/MS/MS	HPLC/MS/MS																
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Curve:		(6 points, not	(6 points, not																

	<table border="1"> <thead> <tr> <th></th> <th>including blank)</th> <th>including blank)</th> </tr> </thead> <tbody> <tr> <td>Precision:</td> <td>1.2 – 4.9 %</td> <td>1.9 – 4.3 %</td> </tr> <tr> <td>Accuracy:</td> <td>-1.3 – 1.5 %</td> <td>-1.3 – 1.0 %</td> </tr> <tr> <td>LLOQ:</td> <td>2 ng/mL</td> <td>1 ng/mL</td> </tr> <tr> <td>ULOQ:</td> <td>200 ng/mL</td> <td>100 ng/mL</td> </tr> <tr> <td>QC1:</td> <td>6.00 ng/mL</td> <td>3.00 ng/mL</td> </tr> <tr> <td>Precision:</td> <td>5.7 %</td> <td>3.3 %</td> </tr> <tr> <td>Accuracy:</td> <td>-5.2 %</td> <td>-5.0 %</td> </tr> <tr> <td>QC2:</td> <td>20.0 ng/mL</td> <td>10.0 ng/mL</td> </tr> <tr> <td>Precision:</td> <td>3.1 %</td> <td>2.7 %</td> </tr> <tr> <td>Accuracy:</td> <td>-6.0 %</td> <td>-3.5 %</td> </tr> <tr> <td>QC3:</td> <td>160.0 ng/mL</td> <td>80.0 ng/mL</td> </tr> <tr> <td>Precision:</td> <td>1.4 %</td> <td>2.7 %</td> </tr> <tr> <td>Accuracy:</td> <td>-5.6 %</td> <td>-4.6 %</td> </tr> </tbody> </table> <ul style="list-style-type: none"> Bioanalytical site: Non-Clinical Safety Research, Department of Bioanalysis, H. Lundbeck A/S, (b) (4) Lu AF39732 and Lu AF39655 as internal standards for CLB and N-CLB, respective. <p>Comments:</p> <ul style="list-style-type: none"> The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <15%. Following the OSI inspection, no objectionable conditions were observed and no Form FDA 483 was issued. It was recommended that the clinical and bioanalytical portions of study 14033A be accepted for review. 		including blank)	including blank)	Precision:	1.2 – 4.9 %	1.9 – 4.3 %	Accuracy:	-1.3 – 1.5 %	-1.3 – 1.0 %	LLOQ:	2 ng/mL	1 ng/mL	ULOQ:	200 ng/mL	100 ng/mL	QC1:	6.00 ng/mL	3.00 ng/mL	Precision:	5.7 %	3.3 %	Accuracy:	-5.2 %	-5.0 %	QC2:	20.0 ng/mL	10.0 ng/mL	Precision:	3.1 %	2.7 %	Accuracy:	-6.0 %	-3.5 %	QC3:	160.0 ng/mL	80.0 ng/mL	Precision:	1.4 %	2.7 %	Accuracy:	-5.6 %	-4.6 %
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QC3:	160.0 ng/mL	80.0 ng/mL																																									
Precision:	1.4 %	2.7 %																																									
Accuracy:	-5.6 %	-4.6 %																																									
Population/ Demographics	N=30 enrolled (N=15 for AB or BA; male:female = 4:1), treated, and completed the study.																																										
PK Results	<p>Figure 1. Mean (SD) plasma concentration-time profiles of clobazam (top figure) and N-CLB (bottom figure) following single-doses of clobazam oral suspension and tablet</p>																																										



● Treatment A: 20 mg CLB suspension; ○ Treatment B: 20 mg CLB tablet.

Table 1. Summary of pharmacokinetic parameters and statistical analysis for clobazam

Pharmacokinetic Parameter	CLB Suspension (Treatment A) (N=30)	CLB Tablet (Treatment B) (N=30)	Geometric Mean Ratio [90% CI] ^b
AUC _{0-inf} (ng•h/mL)	10227 (2897)	10261 (2781)	0.995 [0.976, 1.01]
AUC _{0-t} (ng•h/mL)	10007 (2806)	10032 (2732)	0.997 [0.977, 1.02]
C _{max} (ng/mL)	421 (86.1)	354 (71.4)	1.19 [1.12, 1.27]
T _{max} (h) ^a	0.750 (0.500, 2.00)	2.00 (1.00, 4.00)	
t _{1/2} (h)	39.7 (14.9)	38.9 (13.8)	
CL/F (L/h)	2.12 (0.635)	2.10 (0.622)	
V _z /F (L)	112 (24.3)	110 (24.2)	

a. All data presented as arithmetic mean (SD), except for T_{max} (median (min, max))

b. Based on geometric means

Table 2. Summary of pharmacokinetic parameters and statistical analysis for N-CLB

Parameter	Treatment A 20 mg Clobazam Suspension N=17	Treatment B 20 mg Clobazam Tablet N=24
AUC _{0-inf} (ng•h/mL)	13,087 (6175)	14,668 (7466)
AUC _{0-t} (ng•h/mL)	12,085 (4803)	12,822 (5218)
C _{max} (ng/mL)	79.6 (24.5)	79.4 (25.0)
t _{max} (h)	48.0 (36.0, 120)	48.0 (12.0, 120)
t _{1/2} (h)	59.5 (23.1)	72.3 (34.3)

Note: All data presented as arithmetic mean (SD), except for T_{max} (median (min, max)). Cases where pre-dose plasma concentrations greater than 5% of C_{max} were not included in the statistical analysis.

Safety

- No death, SAEs, withdrawal, or clinical abnormality.
- Two (6.7%) subjects reporting 3 AEs after CLB suspension and 2 (6.7%)

	subjects reporting 2 AEs after CLB tablet. No AE occurred in >1 subject.
Conclusions	<ul style="list-style-type: none"> • The shapes of curves of CLB were similar from both formulations. However, Absorption of CLB occurred more rapidly after suspension administration than after tablet administration. Mean median Tmax for CLB following oral suspension and tablet administration were 0.75 hours and 2 hours, respectively. • The point estimates and corresponding 90% CIs for the geometric mean ratios for the exposure measures (AUC0-inf and AUC0-t) between CLB oral suspension and oral tablets were within the BE acceptance criteria of 80-125%. • For Cmax, the oral suspension was approximately 19% higher than that from oral tablet, whereas the upper bound of the 90% CI (i.e., 1.27) fell outside of the upper limit of the acceptance BE criteria. However, this difference is not considered clinically significant. • Results indicate that CLB oral suspension is bioequivalent to the reference CLB oral tablets. • Similar safety profiles between two formulations were reported. • 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 ~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.
Comments	<ul style="list-style-type: none"> • The observed pharmacokinetic properties are consistent in general with those reported for clobazam tablets (refer to the approved Onfi labeling for details describing absorption, distribution, metabolism and elimination). • Since CLB is dosed with up-titration, is intended for chronic administration and has been reported to be safe and well tolerated for up to 160 mg (tablet), the higher Cmax by 19% is considered clinically insignificant.

4.3 OCP Filing/Review Form

Office of Clinical Pharmacology			
<i>New Drug Application Filing and Review Form</i>			
<u>General Information About the Submission</u>			
	Information		Information
NDA/BLA Number	203993	Brand Name	Onfi™
OCP Division (I, II, III, IV, V)	DCP-1	Generic Name	Clobazam
Medical Division	HFD-120	Drug Class	Anticonvulsant
OCP Reviewer	Ta-Chen Wu, Ph.D.	Indication(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ≥ 2 years of age
OCP Team Leader	Angela Yuxin Men, M.D., Ph.D.	Dosage Form	Suspension: 2.5 mg/mL
Pharmacometrics Reviewer	None	Dosing Regimen	ONFI should be administered in divided doses twice daily, dosed according to body weight (the 5 mg dose can be administered as a single daily dose). <u>≤ 30 kg Body Weight:</u> <ul style="list-style-type: none"> • Starting dose: 5 mg • Starting Day 7: 10 mg • Starting Day 14: 20 mg <u>> 30 kg Body Weight:</u> <ul style="list-style-type: none"> • Starting dose: 10 mg • Starting Day 7: 20 mg • Starting Day 14: 40 mg
Pharmacogenomics Reviewer	None		
Date of Submission	02/28/2012	Route of Administration	Oral
Estimated Due Date of OCP Review	10/15/2012	Sponsor	Lundbeck ILC
Medical Division Due Date	10/29/2012	Priority Classification	S
PDUFA Due Date	12/28/2012		
<i>Clin. Pharm. and Biopharm. Information</i>			
<u>Summary:</u> ONFI (clobazam) Tablets (5, 10, and 20 mg strengths) were approved on 21 October 2011 (NDA 202067) in the US for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS). The applicant seeks approval for a new oral suspension formulation targeted for LGS patients who have difficulty swallowing tablets.			

The current NDA submission contains a relative bioavailability (BA) study (Study 14033A) comparing an oral suspension formulation (2.5 mg/mL) to the approved 20 mg tablet to support the approval. In addition, the applicant provides a statistical analysis of in-vitro binding data for clobazam and N-desmethyloclobazam (Study 176-808-2012) to support a more robust Mechanism of Action statement in the included proposed labeling. No study was conducted by the Applicant to evaluate the potential food effect on BA of oral suspension.

Clinical pharmacology development program

Type of Study	Study Identifier	Objectives(s) of the Study	Study Design & Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Exposed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
BA	14033A	Assess the relative bioavailability, safety, and tolerability of a single 20 mg oral dose of clobazam (CLB) administered as a suspension as compared to a CLB 20 mg oral tablet	Open label, randomized, single-dose, 2 way crossover	Oral CLB tablet: 20 mg Oral CLB suspension: 20 mg	CLB 20 mg tablet: 30 CLB 20 mg suspension: 30	Healthy subjects	Two single doses separated by a 14 day drug free period

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Sponsor provided Word and PDF version, both clean and with track-changes, for the proposed labeling
Reference Bioanalytical and Analytical Methods	X			A validated LC/MS/MS method: Validation: Report 14210 Individual study: Report 14200
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			Study 14033A (Tablets as reference), conducted under fasted condition
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				No food-effect study was conducted.
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Request for ped waiver in neonates (birth to 1 month of age) and infants (1 month up to 2 years of age)
Literature References	X			7
Total Number of Studies	2	2	4	Study 14033A + Validation report + Literature

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			N/A	Only 1 relative BA study with TBM formulation
2	Has the applicant provided metabolism and			N/A	Labeling information

	drug-drug interaction information?				
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	Yes			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	Yes			
5	Has a rationale for dose selection been submitted?	Yes			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	Yes			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	Yes			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	Yes			Bioanalytical report provided separately without hyperlinking from the study report
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			N/A	No prior pre-submission discussions occurred for this application
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			N/A	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	Yes			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			N/A	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			N/A	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			N/A	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			N/A	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			N/A	
17	Is there adequate information on the	Yes			

	pharmacokinetics and exposure-response in the clinical pharmacology section of the label?				
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	(Yes)			Effect of food will need to be evaluated for the new formulation so it can be taken without regard to food like the approved Tablets
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		No		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

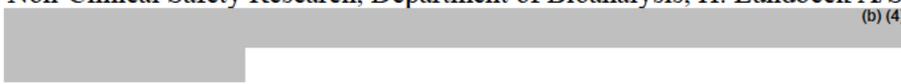
Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- We noticed that effect of food has not been evaluated for the proposed new formulation. Given the labeling recommendation for the oral tablets, please address how oral suspension will be administered with regard to food intake.
- Please provide a “definition” file in PDF format for the electronic datasets for Study 14033A.

We request a DSI inspection of the clinical and the analytical sites for the following study (Study 14033A (relative bioavailability study)):

Clinical site: SeaView Research, Miami, U.S.A. (Investigator: Axel Juan, MD)

Analytical site: Non-Clinical Safety Research, Department of Bioanalysis, H. Lundbeck A/S, (b) (4)



Ta-Chen Wu

Reviewing Clinical Pharmacologist

Date

Angela Yuxin Men

Team Leader/Supervisor

Date

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

/s/

TA-CHEN WU
12/07/2012

YUXIN MEN
12/08/2012