

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203993Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	December 12, 2012
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	203993
Supplement#	
Applicant	Lundbeck Inc.
Date of Submission	February 28, 2012
PDUFA Goal Date	December 28, 2012
Proprietary Name / Established (USAN) names	Onfi Oral Suspension / Clobazam
Dosage forms / Strength	2.5 mg/mL
Proposed Indication(s)	Lennox-Gastaut Syndrome (LGS) in patients ≥ 2 years of age
Recommended:	Approval

1. Introduction and Background

Clobazam (Tablets (Onfi) is a benzodiazepine that has recently (October 21, 2011) been approved for adjunctive treatment of patients with Lennox Gastaut Syndrome (LGS) who are 2 years of age and older. Previously it had been approved for the treatment of anxiety and epilepsy in over 100 countries. LGS is a relatively uncommon and serious epileptic syndrome that begins at about ages 3-8 years of age, and is associated with multiple seizure types including, “drop seizures,” which are considered dangerous in nature. This Division’s approval of Onfi Tablets was based upon two pivotal well controlled studies, the primary endpoint being the percent reduction in the weekly average frequency of “drop seizures.” The Sponsor now submits an application for an oral suspension formulation. The evidence that the Sponsor is submitting for approval is the bioequivalence of the new suspension formulation to the already marketed tablet. The Sponsor believes that this new formulation is more easily administered to patients who have difficulty swallowing whole or crushed¹ tablets due to young age or the neurologic disability associated with LGS.

There are currently, five other antiepileptic drugs (AEDs) approved for seizures associated with LGS. These include clonazepam, felbamate, lamotrigine, topiramate, and rufinamide. A number of additional anticonvulsants, which are not specifically labeled for LGS, are used as well, as is a ketogenic diet and vagal nerve stimulation.

2. CMC/Device

The present drug product is a suspension (2.5 mg/mL) packed in a (b) (4) amber glass bottle. It is berry flavored and with the following excipients: magnesium aluminum silicate, xanthan gum, citric acid monohydrate, disodium (b) (4) simethicone, polysorbate 80, methyl and propyl paraben, propylene glycol, (u) (4) solution, and flavoring. The chemistry reviewer, Dr. A. Khairuzzaman, found this application to be acceptable for approval. The manufacturing process, according to the chemist, assures a consistent product of the necessary quality. Chemical stability supports a 24 month shelf life.

The Office of Compliance (OC) has found the manufacturing and testing acceptable.

One area of discussion, pertinent to the labeling of this product, raised by the chemist was that of a potential food effect. The Chemistry reviewer raised the issue that there may be a potential food effect. Thus, the reviewer notes that a food effect study was not provided for the present formulation. Moreover he argued that while a food effect study for the tablet was negative it is possible that the suspension may exhibit a food effect because of differences in API particle size, dissolution and inactive ingredient content in the suspension drug product, such as surfactant. This was communicated to the Sponsor and discussed with OCP (see

¹ According to the present Onfi label crushed tablets may be administered mixed with applesauce.

below). The chemistry reviewer deferred the final decision to OCP and the clinical staff (see below).

3. Nonclinical Pharmacology/Toxicology

No issues were identified.

4. Clinical Pharmacology/Biopharmaceutics

Dr Ta-Chen Wu performed the primary OCP review, and Dr. Angela Men was the OCP team leader.

The therapeutic efficacy of the present clobazam product is based upon an open-label, randomized, two-way crossover study (Study 14033A), conducted under fasted conditions, that compared the bioavailability of clobazam administered as the suspension (Test) or the tablet in a single 20 mg oral dose. This single center study examined a total of 30 healthy adult men and women.

A summary of the results of the bioequivalence study are presented in the table below (transcribed from the OCP review);

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]

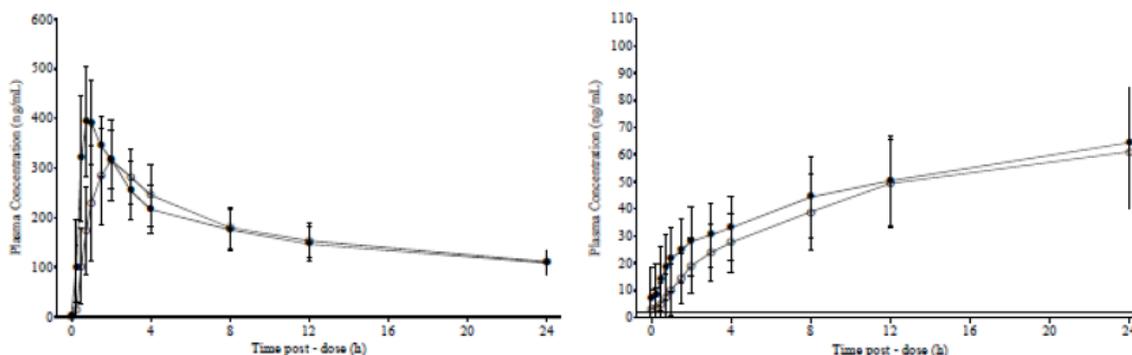
a. All data presented as Geometric LSM, except for T_{max} (median (min, max))

b. Based on geometric means

AUCs proved to meet bioequivalence standards. C_{max} was only marginally outside the range. Thus, the upper confidence interval criteria for the geometric mean ratio for bioequivalence should be 1.25; the present upper range was determined to be 1.27. This small difference was not thought to have a clinically significant impact.

The T_{max} differed by only a modest amount: i.e. the mean T_{max} for the suspension was 0.75 hours, whereas that for the tablet was 2.0 hours.

Clobazam is metabolized into an active metabolite, nor-clobazam. The figure below (Transcribed from the OCP review) presents a comparison of the tablet (closed circles) and suspension (open circles) for the mean concentrations (\pm SD) curves for both clobazam (left figure) and nor clobazam (right figure). The curves were similar when comparing both formulations to each other for both clobazam nor-clobazam.



In conclusion while a modest difference was observed (slightly increased Cmax), this difference was not thought to be clinically significant. I concur with this determination.

OSI's inspections were found acceptable.

As noted above, the Sponsor did not provide a food effect study for the present formulation. The CMC reviewer believed a food effect may be possible, notwithstanding the absence of such an effect for the tablet. Chemistry, however, deferred to OCP and DNP for a final decision. In their review OCP concludes that a significant food effect is unlikely. This was based upon a number of factors. Thus, they argue that there is an absence of a significant food effect of the tablet. Moreover, they note that if a food effect were to occur that such an effect would be to increase absorption, and because of the already high bioavailability this would not be of a significant magnitude. The reason for the potential of theoretical increase in absorption with food is two-fold: 1) surfactant excipients may increase bioavailability in the presence of food compared to the tablet, 2) the behavior of the potential BCS class (class II) may be expected to show an increase in absorption with food. OCP concludes 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." No labeling restrictions or additional studies were requested. This reviewer agrees.

5. Clinical Microbiology

As per the micro reviewer, S. Donald, antimicrobial effectiveness stability studies of the formulation supports a 90 day stability of an opened bottle.

6. Clinical/Statistical- Efficacy

No new efficacy studies are submitted. The demonstration of efficacy is based upon a single bioequivalence study (see above).

7. Safety

Dr Sheridan, DNP Medical Reviewer, performed the safety review.

The only new safety data provided is that provided from the single-dose relative bioavailability study used to demonstrate the bioequivalence between the proposed Onfi™ oral suspension and the current marketed tablets (20-mg strength) and interim post-marketing reporting.

The study, described above, exposed a total of 30 patients to two single dose of 20 mg of clobazam in both the tablet and suspension formulation. Exposures were separated by a 14 day washout period.

No deaths serious adverse events or discontinuations were noted in the study. A total of 5 adverse events were reported in 5 patients, 2 subjects receiving tablets and 3 receiving suspension. The adverse events are described in the table below: Four of the events were categorized as mild and one as moderate (presyncope).

Preferred Term	Number of Subjects (% Subjects) with Adverse Events	
	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.

No significant vital sign, EKG, blood chemistry, suicidal evaluation (using the C-SSRS) signal was observed.

Dr Sheridan does not believe there are any new significant safety signals. Thus, while this study was too small and too short in duration to conclude anything definitive regarding the new formulation, no new obvious safety signal could be appreciated. Moreover, the safety may be adequately extrapolated from the demonstration of bioequivalence.

Dr. Sheridan also notes that there are no new safety signals based upon periodic Safety Update Reports submitted since October 2011.

8. Advisory Committee Meeting

Not Applicable.

9. Pediatrics

PREA is not applicable as the indication is an Orphan Indication.

10. Other Relevant Regulatory Issues

As noted above, the evidence provided for approval consisted of a single bioequivalence study. According to Dr. Sheridan the Sponsor has provided financial disclosure, which provides evidence for the absence of significant conflict of interest for the investigator who performed this study (e.g., no proprietary interest in the product etc).

11. Labeling

12.

Please see the label accompanying the action letter.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval
- Risk Benefit Assessment: Similar to the approved tablet.
- Recommendation for Postmarketing Risk Management Activities: None
- Recommendation for other Postmarketing Study Commitments: None

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/s/

NORMAN HERSHKOWITZ
12/12/2012