© Copyright 2012 Oregon State University. All Rights Reserved

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: May 2012
Generic Name: clobazam
PDL Class: Oral Anticonvulsants

End date of literature search: April 2012
Brand Name (Manufacturer): Onfi™
Dossier Received: Yes

FDA Approved Indications: Clobazam is a benzodiazepine indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older.[1]

Conclusions:
Head to head comparative evidence is lacking for the treatment of LGS and optimal medical therapy is uncertain. Valproate may be first-line treatment based on NICE guidance and consensus guidelines. Antiepileptic drugs (AEDs) approved as adjunctive therapy for LGS include lamotrigine, topiramate, rufinamide, felbamate, and now clobazam. There is low to moderate quality evidence that adjunctive therapy with clobazam may reduce drop seizures in patients with LGS.

Recommendations:
Make clobazam a non-preferred oral anticonvulsant agent on the preferred drug list (PDL) and include a prior authorization restricting use to adjunctive treatment for the FDA approved indication of Lennox-Gastaut in patients 2 years of age and older (Appendix 2).

Background: LGS is an epilepsy syndrome characterized by multiple seizure types, cognitive impairment, and specific electroencephalogram (EEG) features.[2,3] Age of onset is most commonly between 3 and 10 years, with commonly a history of infantile spasms. Long-term prognosis for both neurocognitive outcomes and seizure control is poor. It is a rare syndrome and requires input from specialists with expertise in the area. Recent updated guidelines from the National Institute for Clinical Excellence (NICE) identify seizure freedom, at least 50% reduction in seizure frequency, and withdrawals due to adverse events to be the most important outcomes in evaluating LGS.[2] The NICE guidance recommends sodium valproate as first-line treatment to children with LGS. This recommendation however is based on extrapolated evidence from idiopathic generalized epilepsy and consensus guidelines. There is limited comparative evidence evaluating treatment in LGS. Lamotrigine is recommended as adjunctive treatment if sodium valproate is ineffective or not tolerated (based on two low quality placebo controlled trials demonstrating lamotrigine to be more effective in reducing at least 50% the seizure frequency). If adjunctive treatment is ineffective, the NICE guidance recommends that rufinamide and topiramate may be considered by a specialist if adjunctive treatment is ineffective (based on low quality evidence).[2] Felbamate is recommended as last line therapy after all other therapy has shown to be ineffective or not tolerated. Carbamazepine, gabapentin, oxcarbazepine,

pregabalin, tiagabine, and vigabatrin should not be offered for LGS because clinical practice suggests seizures can be aggravated by these medications.[2,3]

Clobazam was FDA approved in the United States in 2011 based on data from two multicenter studies.[4,5] As clobazam is indicated to treat a disease or condition that affects fewer than 200,000 people in the United States, it was granted orphan drug designation by the FDA. This is the sixth medication approved for LGS in the United States. It is a 1,5 benzodiazepine (the only representative of that class in clinical use today) and is a federally controlled schedule four substance (C-IV).[6] Clobazam has also been studied off-label in patients with partial epilepsy and as monotherapy for childhood epilepsy.[6]

Clinical Efficacy:

Clobazam was evaluated in one phase II dose ranging study and one fair quality fair phase III efficacy study.[4, 5] Details of these are included in the evidence table below. The pivotal phase III trial (COMTAN)[5] was a fair quality study evaluating the efficacy and safety of three doses of clobazam (0.25-, 0.5-, and 1.0-mg/kg/day) compared to placebo as adjunctive therapy for LGS. Approximately 50% of all patients were receiving concomitant valproate. All of treatment arms, 0.25-, 0.5-, and 1.0-mg/kg/day, had a significantly greater decrease in average weekly rate of drop seizures from baseline compared to placebo. Mean differences from the placebo group were 29.1%, 37.3%, and 56.1% for the low-, medium-, and high-dosage groups with a linear trend ($p<0.0001$) of increasing efficacy with increasing dosage. The effect on nondrop seizures was not significant. Responder rates increased with increasing clobazam dosages and there was a statistically significant increase over placebo in the 0.5- ($p=0.0159$, OR 2.8; 95% CI 1.2 to 6.5) and 1.0mg/kg/day ($p<0.0001$, OR 7.5; 95% CI 3.0 to 18.5). An overall attrition rate of 25.6% occurred in the trial (30.5% in placebo group vs. 13.8%, 27.4%, and 30.5% in the 0.25-, 0.5-, and 1.0 mg/kg/day groups, respectively). 21 participants were excluded from the intention to treat population for primary efficacy analysis who did not have ≥ 1 daily seizure measurement during the maintenance period. There was also a potentially relevant difference in baseline mean average weekly drop seizure rate between the groups, potentially causing a less severe group of patients in the 0.5 mg/kg/day group compared to the others.

A second phase II, dose-ranging study compared a total of 68 patients on either high dose clobazam (target dose of 1mg/kg/day) or low dose clobazam (target dose 0.25 mg/kg/day). At baseline, patients were on stable doses of 1-3 AEDs and had at least 2 drop seizures per week. From baseline to maintenance, the percentage change in drop seizures was significant in both the low-dosage ($12 \pm 122\%$, $p = 0.0162$) and high-dosage groups ($85 \pm 16.8\%$, $p < 0.0001$). The reduction was also significantly greater in the high dosage group when compared with the low-dosage group. Responder rate was significantly greater in the high dosage group versus the low dosage group (83% vs. 38%, $p=0.0001$; RR 0.46; 95% CI (0.3 to 0.7). However, this trial included some potentially fatal flaws in design and results should be interpreted with caution. It was unclear if appropriate methods for generation of randomization sequence and allocation concealment were used, an unblinded physician adjusted the dose during the taper period, and there was a lack of specific information to compare baseline characteristics of participants.

Adverse events occurred with >10% difference between placebo and clobazam were somnolence, pyrexia, lethargy, drooling, and constipation. Somnolence and drooling increased in frequency with increasing dosage. There was also a dosage-related trend observed for the overall incidence of adverse events (AEs) leading to discontinuation with a statistically significant difference between the high dose clobazam group compared to placebo (20.3% vs. 3.4%, p=0.005; RR 6.0, 95% CI 1.4 to 38.4). Nine patients had pneumonia reported as a serious adverse event during the trial. The authors further detailed that 4 of these patients had either a history of gastroesophageal reflux disease or G-tube placements. Currently an open label extension is underway to further assess the long-term safety of clobazam in patients with LGS.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Seizure Freedom
2) Proportion of participants experiencing at least a 50% reduction in seizure frequency (responders)
4) Withdrawals due to adverse effects

Primary Study Endpoint:

1) Percent decrease in average weekly rate of drop seizures from the 4-week baseline period to the maintenance period vs. placebo (CONTAIN)
2) Percent reduction in drop seizures rate within each treatment group (phase II study).

Ref./ Study Design	Drug Regimens	Patient Population	N	Duration	Efficacy Results	ARR / NNT[ch]	Safety Results (CI, p-values)	ARI / NNH	Quality Rating; Comments
CONTAIN									Quality Rating: Fair;
Ng, et al., [5]DB, PC	T: clobazam 0.25 mg/kg/day T2: clobazam 0.5 mg/kg/day T3: clobazam 1.0 mg/kg/day C: Placebo	Mean Age: 12.4 yrs Range (2-54) Male: 60.5% White: 61.8% currently on ≥ 1 AED's Exclusion criteria: receiving felbamate, unstable hepatic, renal, CV, pulmonary or GI disease, h/o of poor compliance	N=305 Randomized =238 mITT =217 T: 58 T2: 62 T3: 59 C: 59	Outcome assessed @ 15 weeks Trial consisted Of 4 wk baseline phase + 3 wk dose titration phase + 12 weeks maintenance phase	<u>% decrease in mean weekly drop seizure rates:</u> T: -41.2% T2: -49.4% T3: -68.3% C: -12.1% P=0.0120, T v C P=0.0015, T2 v C P<0.0001, T3 v C <u>Responder rates:</u> T: 23 (43.4%) T2: 34 (58.6%) T3: 38 (77.6%) C: 18 (31.6%) P=0.735, T v C OR 0.68; 95% CI (0.3-1.3) P=0.0159, T2 v C OR 0.36; 95% CI (0.16-0.8) P<0.0001, T3 v C OR 0.24; 95% CI (0.1-0.56) <u>Patients who were seizure free</u> T: 5 (7.5%) T2: 7 (12.1%) T3: 12 (24.5%) C: 2 (3.5%) P=0.24, T v C OR 0.37; 95% CI (0.048-2.3) P=0.1, T2 v C OR 0.0.28; 95% CI (0.038-1.5) P=0.005, T3 v C OR 0.14; 95% CI (0.02-0.7)	NA T v C ; NS T2 v C ARR: 27% NNT: 4 T3 v C ARR: 46% NNT: 3 NS	<u>Withdrawals due to Adverse events:</u> T: 4 (6.9%) T2: 8 (12.9%) T3: 13 (20.3%) C: 2 (3.4%) P = NS; T v C and T2 v C P=0.005; T3 v C RR: 6.0; 95% CI (1.3 -38.4)	T v C; NS T1 v C; NS T2 v C: ARI 16.9% NNH: 6	**Internal Validity:** <u>Selection- Central</u> randomization through interactive voice response system. Study protocol revised after 81 patients enrolled due to many premature discontinuations and entry into the open label extension <u>Performance</u>- matching placebo tablets used to account for blinding <u>Detection</u> – unclear blinding of evaluators <u>Attrition</u> - Overall attrition rate of 25.6% 21 participants (8.8%) initially randomized not included in mITT population and analysis and almost half of them (n=10) were excluded from the high dose clobazam group **External Validity:** Recruitment – not reported Patient Characteristics –Baseline mean average weekly drop seizure rate overall was 86.6, but differed between groups (only 58.8 in clobazam 0.5mg/kg/, and 98.1 in 0.25mg/kg/day group
Phase II, Dose Ranging									

Conry, et al.[4] Phase II, dose rating study	T1: clobazam 0.25 mg/kg/day T2: clobazam 1.0 mg/kg/day	Median Age: 7.4 yrs LGS on 1-3 AEDs at least 2 drop seizures per week Exclusion criteria: status epilepticus within 12 weeks, progressive neurologic disease	N=68 mITT =61 T: 32 T2: 36	Outcomes assessed @ 7 weeks Trial consiste Of 4 wk baseline phase + 3 wk dose titration phase + 4 weeks maintenance phase	<u>% decrease in average weekly drop seizure rates:</u> *Low-dose* T1: 12%±122% P=0.0162 *High -dose* T2: 85 ± 16.8% P<0.0001 *High-dose vs. Low-dose* T2>T1; p=0.0001 <u>Responder rates:</u> T1: 12 (38%) T2: 30 (83%) High dose vs. low dose, P=0.0001 RR 0.46; 95% CI (0.3 to 0.7) <u>Patients who were seizure free</u> T1: 2(6%) T2: 8 (22%) P=0.0629 RR 0.28; 95% CI (0.042 to 1.3)	NA ARR 45% NNT 2.2 NS	<u>Withdrawals due to Adverse events:</u> T1: 3 (10%) T2: 6(19%) P=NS RR 1.8; 95% CI (0.4 to 8.6	NS	Quality Rating: Poor **Internal Validity:** <u>Selection-</u> Unclear on randomization generation sequence. Unclear if appropriate method for allocation concealment <u>Performance</u>- An unblinded physician adjusted the patient's dose during the taper period <u>Detection</u> – unclear blinding of evaluators <u>Attrition</u> - Efficacy analysis used a modified intent-to-treat population, which excluded 7 patients from efficacy analysis (10%) Total attrition rates: 15% o T1: 4 (12.5%) o T2: 6 (16.7%) **External Validity:** Recruitment – not reported Patient Characteristics – Baseline characteristic data not provided, median age of 7.4 years appropriate

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

References:

1. Onfi Prescribing Information. Lunbeck Inc. Available at: http://www.medscape.com/infosite/onfi/public.

2. National Institute for Health and Clinical Excellence (NICE). National Clinical Guideline Centre. Pharmacological Update of Clinical Guideline 20. The diagnosis and management of the epilespsies in adults and children in primary and secondary care. 2012.

3. Lennox-Gastaut syndrome. In DynaMed [database online]. EBSCO publishing. 2012. Available at: http://search.ebscohost.com.liboff.ohsu.edu/login.aspx?direct=true&site=DynaMed&id=113862.

4. Conry JA, Ng Y-T, Paolicchi JM, et al. Clobazam in the treatment of Lennox-Gastaut syndrome. *Epilepsia*. 2009;50(5):1158–1166.

5. Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. *Neurology*. 2011;77(15):1473–1481.

6. Onfi Dossier. Evidentiary Submission for Formulary Consideration of Onfi (clobazam) Tablets. Lundbeck Inc.

Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY[1]

Clobazam is a long-acting 1,5-benzodiazepine, the only representative of that class in clinical use today. The exact mechanism of action for clobazam, a 1,5-benzodiazepine, is not fully understood but is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the GABAA receptor.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	100%
Protein Binding	80-90%
Elimination	11% in feces and 82% urine
Half-Life	36-42 hours
Metabolism	Liver; primarily CYP3A4

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Clobazam 5mg, 10mg, or 20mg	Oral	Twice daily (the 5 mg dose can be administered as a single daily dose)	≤30kg: initiate at 5 mg daily and titrate as tolerated up to 20 mg daily >30kg: initiate at 10 mg daily and titrate as tolerated up to 40 mg daily	No dose adjustment is required for patients with mild and moderate renal impairment.	There are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of clobazam. Dosing titration should proceed slowly.	Approved for ≥2 y/o	Starting dose 5 mg/day. Titrated to half the normal dose, as tolerated.	• Reduce dose, or discontinue drug, gradually. • Tablets can be administered whole, or crushed and mixed in applesauce. • Dose escalation should not proceed more rapidly than weekly, because serum concentrations of clobazam and its active metabolite require 5 and 9 days, respectively, to reach steady-state.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications): None

Warnings and Precautions:

Somnolence or Sedation: Clobazam causes somnolence and sedation. In clinical trials, somnolence or sedation were reported at all effective doses and were dose-related. In general, somnolence and sedation begin within the first month of treatment and may diminish with continued treatment. Prescribers should monitor patients for somnolence and sedation, particularly with concomitant use of other central nervous system depressants. Prescribers should caution patients against engaging in hazardous activities requiring mental alertness, such as operating dangerous machinery or motor vehicles.

Withdrawal: Abrupt discontinuation of clobazam should be avoided. Clobazam should be tapered by decreasing the dose every week by 5-10 mg/day until discontinuation. The risk of withdrawal symptoms is greater with higher doses. Withdrawal symptoms (e.g., convulsions, psychosis, hallucinations, behavioral disorder, tremor, and anxiety) have been reported following abrupt discontinuance of benzodiazepines.

Physical and Psychological Dependence: Patients with a history of substance abuse should be under careful surveillance.

Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs), including clobazam, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Look-alike / Sound-alike (LA/SA) Error Risk Potential: Clobazam may be confused with clonazePAM.

Appendix 2: Suggested PA Criteria

Clobazam (Onfi®)

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization: 12 months

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the client have a diagnosis of Lennox-Gastaut syndrome and is 2 years of age or older?	Yes: Go to #3.	No: Pass to RPH; Deny (medical appropriateness)
3. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication?	Yes: Approve for 12 months.	No: Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

• Clobazam is not indicated for other epilepsy syndromes other than Lennox-Gastaut.

DUR/P&T Board Action: 5/31/12 (MH)
Revision(s):
Initiated:

Author: M. Herink, Pharm.D.