Onfi® (clobazam)

Brand Name: Onfi ®

Generic Name: clobazam

Manufacturer: Lundbeck Inc.

Drug Class: Benzodiazepine

Labeled Uses: Clobazam is used as adjuvant treatment of seizures from Lennox-Gastaut Syndrome. [1,2]

Non-labeled Uses: Clobazam is used for catamenial epilepsy and monotherapy in epilsepsy. [2]

Mechanism of Action: Clobazam is a 1,5 benzodiazepine which binds to benzodiazepine receptors on the post synaptic GABA neuron at several sites within the central nervous system. Increased neuronal membrane permeability to chloride ions causes the potentiation of the inhibitory effect of GABA on neuronal excitability. Hyperpolarization and stabilization occur due to the shift in chloride ions. [1,2]

Pharmacokinetics: The pharmacokinetics of Clobazam are linear. See table 1 below.

Table 1. Pharmacokinetic parameters of Clobazam

	Clobazam	**N-desmethylclobazam**
Tmax (hr)	30 minutes to 4 hours [2,3,4]	
Volume of Distribution (L)	100 L [1,3,4]	
$T_{1/2}$	36-42 hours [2,3,4]	71 – 82 hours [2,3,4]
Protein Binding	80% to 90% [1,2,4]	70% [3,4]
Bioavailability	87% [4]	

Metabolism: Clobazam is extensively metabolized by the liver via CYP3A4 and to a lesser extent via CYP2C19 and CYP2B6. [2,3] The active metabolite, N-desmethylclobazam, is extensively metabolized by CYP2C19and displays ~20% activity of Clobazam. [1,2,3,4]

Clobazam has activity as a CYP3A4 inducer and CYP2D6 inhibitor.

Elimination: Excretion of Clobazam is primarily through the kidneys in the urine (82%). 11% of the drug is excreted in the feces. [1,2,3,4]

Efficacy:

Ng YT, Conry JA et al. Randomized, phase III study results of clobazam in Lennox-Gastaut Syndrome. Neurology. 2011;37(15):1473-1481.

Study Design: The CONTAIN study was a phase III, multicenter, randomized, double-blind, placebo-controlled trial.

Study Description: All 238 subjects were randomized to receive either placebo or clobazam 0.25, 0.5 or 1.0 mg/kg/day for 12 weeks. Patients were between the ages of 2- 60 and were diagnosed with Lennox-gastaut syndrome before they were 11 years old. The primary outcome measure of the study was percentage decrease in the average weekly rate of drop seizures from baseline. The secondary outcome measures included percentage decrease in average weekly rate of non-drop seizures and total (drop and nondrop) seizures, responder rates, and global evaluations of the patients overall changes in symptoms over time.

The mean percentage decrease in average weekly rate of drop seizures from baseline was 12.1% for placebo and 41.2% (P = 0.0120), 49.4% (P=0.0015), and 68.3% (P<0.0001) for clobazam 0.25,0.5, and 1.0 mg/kg/day respectively. The mean percentage decrease in average weekly rate of total (drop and non-drop) seizures was 9.3% for placebo and 34.8% (P=0.0414), 45.3% (P=0.0044), and 65.3% (P<0.0001) for clobazam groups: 0.25, 0.5, and 1.0 mg/kg/day. The percentage of patients who achieved a ≥25% response in their drop seizures was 64.2%, 79.3%, and 83.7% for 0.25, 0.5 and 1.0 mg/kg/day in the clobazam groups compared to 49.1% for the placebo group. All groups had improvements in global evaluations of patients overall changes in symptoms from baseline.

Limitations: Lundbeck funded and supported the study. Dr. Ng served as an investigator for Lundbeck and has received funding from the company. The study was unclear in specifically stating what other medications patients were taking to control seizures. The 15 week trial was not sufficient to determine long term efficacy of using clobazam as adjuvant therapy for Lennox-Gastaut Syndrome. Seizure frequency was based on patient reporting which could be inaccurate if seizures were not witnessed or recorded. The criteria for drop seizure was complex and unclear if patients or caregivers received training prior to initiation of the trial .

Conclusions: This study supports that clobazam may be effective as adjunctive therapy in reducing weekly drop seizures in patients with Lennox-Gastaut syndrome compared to placebo.

Conry JA et al. Clobazam in the treatment of Lennox-Gastaut Syndrome. Epilepsia. 2009.50(5):1158-1166.

Study Design: The study was a phase II, multicenter, randomized, double-blind trial.

Study Description: 68 patients were randomized to either low-dose clobazam (5 mg) or high-dose clobazam (10 mg) for 4 weeks. The primary outcome measure was the percent reduction in drop seizure rates from the baseline. 10 of 68 patients enrolled discontinued the study. The mean (± SD) drop seizure

rate per week was reduced from 141 (± 188) to 81 (±122) in the low dose group and 207 (±229) to 32 (±57) in the high dose group. The percentage change from baseline (mean +/- SD) was significant in both the low dose group (12± 122%, P=0.0162) and high dose group (85 ±16.8%, P < 0.0001) The reduction in drop seizure rates was significantly greater in the high-dose group compared with the low dose group (P=0.0001).

Limitations: They study was not compared to placebo or an active control which does not allow for safety or efficacy to be assesed. The 10 week trial was not long enough duration to determine efficacy of clobazam as long-term adjuvant therapy for Lennox-Gastaut Syndrome. Power was not reported in the study and therefore it cannot be determined if the sample size was adequate. Seizure frequency was patient reported which could be inaccurate if seizures were not witnessed or recorded. The study did not state which baseline seizures medications patients were taking.

Conclusions: This study suggests clobazam has a dose related efficacy profile in reducing drop seizure rates when used as adjunctive therapy in patients with Lennox-Gastaut syndrome.

Ng Yu et al. Long-term safety and efficacy of clobazam for Lennox-Gastaut syndrome: Interim results of an open-label extension study. Epilsepsy & Behavior. 2012.25:687-694.

Study Design: The study was a multicenter, open-label extension trial for patients with Lennox-Gastuat syndrome who completed 1 of 2 randomized controlled phase II or phase III trials.

Study Description: Patients that met the inclusion criteria from 2 randomized controlled studies were given the choice of continuing clobazam treatment. Patients from OV-1012 study were given clobazam twice daily starting at a target dose of 0.5mg/kg/day. This dose was given for 48 hours and then adjustments were made per patient needs. Patients from OV-1002 were continued on the same dose from the previous trial or adjustments were made by the unblinded physician. The maximum dose was 80 mg/day. A total of 267 patients were enrolled in the study. The primary outcome measure was the percentage decrease in the average weekly rate of drop seizures at various time intervals compared with baseline values.

A total of 54 patients dropped out of the study for various reasons including lack of efficacy, adverse event, death, or by request from patient or caregiver. The median percentage decreases from baseline in average weekly rate of drop seizures for patients were 71.1% at month 3 and 91.6% at month 24. Adverse events were also monitored throughout the study. 219 (82%) patients experienced ≥ 1 treatment emergent adverse event during the study. The most common adverse events were upper respiratory tract infection

(18.4%), fall (14.2%), pneumonia (13.9%), somnolence (12.7%), otitis media (12.0%), pyrexia (10.5%), and constipation (10.1%).

Limitations: Lundbeck funded and supported the study. Due the study being open label, responder bias may have been present in the study. The study investigators were able to freely add other treatment options and make dosage adjustments which could have influenced results. The development of tolerance to clozabam was not assessed in the study.

Conclusions: This study supports the use of clobazam is safe and efficacious as long term adjunctive therapy in patients suffering from Lennox-Gastaut syndrome. Further studies that are blinded and account for concomitant baseline therapy are needed to fully assess clobazams role in therapy.

Contraindications: Specific contraindications have not been determined in the manufacturers labeling. [1,2,3,4]

Precautions:

- **Withdrawal Symptoms:** Abrupt discontinuation or large decreases in dose can cause rebound or withdrawal symptoms.[1,2,3,4] The following withdrawal symptoms have been reported following abrupt discontinuation: convulsions, psychosis, hallucinations, behavioral disorder, tremor, insomnia, and anxiety.[3] Discontinuation should be gradual to minimize risk of seizures. Due to the long duration of action, an increased risk of withdrawal is possible when switching a patient to a benzodiazepine with a short duration of action.[1] Clobazam should be tapered by decreasing the dose every week by 5-10 mg/day until discontinuation. [1,2,3,4]

- **Physical and Psychological Dependence:** Clobazam is a schedule IV controlled substance and should be used with caution in patients with a history of substance abuse. [1,2,3,4]

- **Somnolence or Sedation:** As with other benzodiazepines, Clobazam can cause drowsiness and dizziness. [1,2,3,4] Somnolence or sedation is more likely to occur with concomitant use of other CNS depressants. [1,2,3,4] Until patients know how the medication affects their cognitive and motor performance they should avoid driving or operating machinery, or other tasks that require mental alertness. [1,2,3] Sedation is most likely to occur within in the first month of initiation of treatment or increased doses and may diminish with continued treatment. [1,3]

- **Suicidal Behavior and Ideation:** Antiepileptic drugs have shown an increased risk of suicidal ideation and behavior in patients receiving these agents for any indication in clinical trials. An analysis of 199 controlled-placebo studies with 27,863 patients in treatment groups and 16,029 patients in placebo groups was conducted. Results showed that 4 suicides occurred in the treatment group and none in the placebo group. Patients in the treatment group were two times more likely to experience suicidal thoughts or behavior.[1,2,3] Health care providers should be

notified immediately if unusual changes in mood or behavior, or suicidal thoughts emerge after the initiation of therapy. [1,2,3]

Adverse Effects: Tables 2 and 3 list the adverse events that occurred in patients treated with Clobazam compared to placebo based on percent of occurrences.

Table 2. Adverse Reactions Reported for >10% of patients in the treatment group compared to placebo

	Clobazam (N=179)	**Placebo (N = 59)**
Central Nervous System		
Somnolence	22%	12%
Lethargy	10%	5%
Respiratory		
Upper respiratory tract infection	12%	10%

Table 3. Adverse Reactions Reported for 1% -10% of patients in the treatment group compared to placebo

	Clobazam (N=179)	**Placebo (N = 59)**
Central Nervous System		
Aggressiveness	8%	5%
Irritability	7%	5%
Ataxia	5%	3%
Fatigue	5%	2%
Sedation	5%	3%
Psychomotor hyperactivity	4%	3%
Gastrointestinal Disorders		
Vomiting	7%	5%
Constipation	5%	0%
Increased Appetite	3%	0%
Dysphagia	2%	0%

Genitourinary Disorders		
Urinary tract infection	4%	0%
Neuromuscular & Skeletal Disorders		
Dysarthria	3%	0%
Respiratory Disorders		
Cough	5%	0%
Pneumonia	4%	2%
Bronchitis	2%	0%

Drug Interactions [1,2,3,4]

Alcohol: May enhance serum concentration of clobazam. May enhance the CNS depressant effect of clobazam.

Antifungal Agents (Azole derivatives): May decrease the metabolism of benzodiazepines.

Aprepitant: May increase the serum concentration of benzodiazepines.

Azelastine: May enhance the CNS depressant effect of Azelastine.

Buprenorphine: May enhance the CNS depressant effect of Buprenorphine.

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of benzodiazepines.

Carbamazepine: May increase the metabolism of benzodiazepines.

Cimetidine: May decrease the metabolism of benzodiazepines.

Clozapine: May increase the adverse or toxic effects of Clozapine.

Codeine: CYP2D6 inhibitors may decrease effect of codeine.

CYP3A4 Inducers: Clobazam may decrease the serum concentration of drugs that are substrates for the CYP3A4 metabolism pathway.

CYP 2D6 Inhibitors: Clobazam may increase the serum concentration of drugs that are substrated for the CYP2D6 metabolism pathway.

Droperidol: May enhance the CNS depressant effect of CNS depressants.

Fosaprepitant: May increase the serum concentration of benzodiazepines.

Grapefruit Juice: May decrease the metabolism of benzodiazepines.

Hydroxyzine: May enhance the CNS depressant effect of CNS depressants.

Isoniazid: May decrease the metabolism of Benzodiazepines.

Macrolide Antibiotics: May decrease the metabolism of benzodiazepines.

Magnesium Sulfate: May enhance the CNS depressant effect of CNS depressants.

Methotrimeprazine: CNS depressant may enhance the CNS depressant effect of methotrimeprazine.

Metyrosine: CNS depressants may enhance the CNS depressant effect of metyrosine.

Mirtazapine: CNS depressants may enhance the CNS depressant effect of mirtazapine.

Olanzapine: May increase the adverse or toxic effects of olanzapine.

Ondansetron: May increase serum concentrations of ondansetron.

Paraldehyde: CNS depressant may enhance effect of CNS depressants.

Phenytoin: May increase the serum concentration of phenytoin.

Pramipexole: May enhance the sedative effect of pramipexole.

Propafenone: May cause increase serum concentrations of propefenone.

Proton Pump Inhibitors: May increase the serum concentrations of benzodiazepines.

Ropinirole: May enhance the CNS depressant effect of CNS depressants.

Rotigotine: May enhance the CNS depressant effect of CNS depressants.

Selective Serotonin Reuptake Inhibitors: May increase the adverse or toxic effects of selective serotonin reuptake inhibitors. May decrease the metabolism of benzodiazepines.

Sodium Oxybate: May enhance the CNS depressant effect of sodium oxybate.

St. Johns Wort: May increase the metabolism of clobazam.

Zolpidem: May enhance the CNS depressant effect of zolpidem.

Dosage Form and Strength: Onfi ® tablets are available in the following strengths: 5 mg, 10 mg, and 20 mg. The tablets are white, round with "LU" on one side and "5", "10", or "20" on the other side.[1,2,3,4] Onfi ® oral suspension is an off- white liquid and is berry flavored.

Administration: Clobazam can be taken with or without food. The tablets may be broken along the score or crushed and mixed into applesauce. The oral liquid formulation should be shaken prior to use and the dose should be squirted into the corner of the patient's mouth.

Dosing: [1,2,3,4]

Adults:

- Lennox-Gastaut Syndrome (adjunctive):

  ≤30 kg: Start 5 mg PO daily for ≥ 1 week, then increase to 5 mg twice daily for ≥ 1 week, then increase to 10 mg twice daily.

  >30 kg: Start 5 mg twice daily for ≥ 1 week , then increase to 10 mg twice daily for ≥ 1week, then increase to 20 mg twice daily.

  Upon discontinuation, the daily dose should be decreased by 5-10 mg/day on a weekly basis.

- Catamenial Epilsepsy (adjunctive): 20-30 mg daily for 10 days during the premenstrual period.

Pediatric:

- Lennox-Gastaut Syndrome (adjunctive): Same as adult dosing
- Epilepsy (monotherapy): Children 2-16 years: Titrate slowly over 1-3 weeks to target dose of ~0.5 mg/kg/day in 2 divided doses.

Geratrics:

- Lennox-Gastaust Syndrome (adjunctive):

  ≤ 30 kg: Start 5 mg PO daily for ≥ 2 weeks, then increase to 5 mg twice daily for ≥ 1 week, then increase to 10 mg twice daily.

  >30 kg: Start 5 mg PO daily for ≥ 1 week, then increase to 5 mg twice daily for ≥ 1 week, then increase to 10 mg twice daily for ≥ 1 week, then increase to 20 mg twice daily.

  Upon discontinuation, the daily dose should be decreased by 5-10 mg/day on a weekly basis.

Renal Impairment: No dose adjustment is necessary for CrCl ≥ 30 ml/min. For CrCl < 30 ml/min no data is available to make a dosage recommendation.

Hepatic Impairment:

- Mild to moderate (Child-Pugh Score 5-9):
  >30 kg: Start 5 mg PO daily. On day 7, increase to 5 mg twice daily. On day 14, increase to 10 mg twice daily. Starting on day 21, increase to a maximum of 20 mg twice daily.

  ≤ 30 kg: Start 5 mg PO daily. On day 14, increase to 5 mg twice daily. Starting on day 21, increase to a maximum of 10 mg twice daily.

- Severe: No dosing recommendations available due to limit data.

Conclusion: The published results from the CONTAIN trial suggest that clobazam is effective as adjuvant therapy in reducing weekly drop seizures in patients with Lennox-Gastuat syndrome. The most commonly seen adverse events reported for clobazam was somnolence, pyrexia, upper respiratory infections, and lethargy. Due to limited data available, clobazam should be used with caution in patients with hepatic or renal failure. Clobazam's role in therapy is yet to be determined. Further studies need to be conducted comparing clobazam to other benzodiazepines to determine if clobazam is more efficacious as adjuvant treatment for seizures in Lennox-Gastaut Syndrome.

Resources:

1. Onfi. Clinical Pharmacology [Internet database]. Gold Standard, Inc., 2012.
2. Onfi. Lexi-Drugs [Internet database]. Lexi-Comp, Inc; 2012.
3. Onfi [package insert]. Deerfield, IL. Lundbeck LLC; 2012.
4. Onfi. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
5. Ng YT, Conry JA et al. Randomized, phase III study results of clobazam in Lennox-Gastaut Syndrome. Neurology. 2011;37(15):1473-1481.

6. Ng Yu et al. Long-term safety and efficacy of clobazam for Lennox-Gastaut syndrome: Interim results of an open-label extension study. Epilsepsy & Behavior. 2012.25:687-694.
7. Conry JA et al. Clobazam in the treatment of Lennox-Gastaut Syndrome. Epilepsia. 2009.50(5):1158-1166.

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