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# Literature Scan: Oral Antiepileptic Drugs

**Month/Year of Review:** March 2015

**Date of Last Review:** May 2014
**Source Document:** OSU College of Pharmacy

**Current Status of PDL Class:**
See **Appendix 1**.

**Current Prior Authorization Criteria:**
See **Appendix 5**.

**Conclusions:**

- There were no new comparative systematic reviews or evidence-based guidelines of antiepileptic drugs (AEDs) identified on which to recommend changes to the PDL class.
- FDA expanded the black-boxed warnings on valproate products to include possible fetal neural tube defects and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations, hypospadias, limb malformations) when used during pregnancy.
- There is insufficient evidence that controlled-release carbamazepine is more effective than the immediate-release formulations; however, low quality evidence suggests the controlled-release formulations may be more tolerable.
- There is insufficient evidence that felbamate is effective as add-on therapy for refractory partial-onset epilepsy.
- There is moderate quality evidence that tiagabine is effective at reducing seizure frequency but is associated with more dizziness, fatigue, nervousness and tremor when used as add-on therapy in patients with localization-related seizures who have failed at least two AEDs as monotherapy.
- There is moderate quality evidence that in the short term, adding pregabalin at doses ranging from 150-600 mg per day to AED therapy can significantly reduce seizure rates and cease seizures altogether in patients with drug-resistant partial epilepsy. There is insufficient evidence, however, for longer treatment duration and insufficient evidence comparing pregabalin against other adjunctive treatments.
- There is moderate quality evidence that in the short term, adding topiramate at doses no greater than 300 mg per day to AED therapy can significantly reduce rates and cease seizures altogether in patient with drug-resistant partial epilepsy. There is insufficient evidence, however, for longer treatment duration and insufficient evidence comparing topiramate against other adjunctive treatments.

**Recommendations**:

- Retire current PA criteria for pregabalin which will be replaced with the PA criteria “Drugs Used for Non-funded Pain Conditions”.
- Remove PA criteria for preferred topiramate products due to cost effectiveness (see **Appendix 5**).
- No further review or research needed at this time. Review comparative drug costs in the executive session.



Author: A. Gibler, Pharm.D.

Date: March 2015

**Previous Conclusions and Recommendations:**

- There were no new comparative systematic reviews or evidence-based guidelines identified on which to recommend changes to the current PDL class.
- FDA safety communications indicate that all valproate products are now contraindicated for pregnant women and ezogabine has a new Boxed Warning about the risk of permanent retinal abnormalities, vision loss and skin discoloration with its use.
- There is insufficient comparative efficacy and safety evidence for eslicarbazepine versus other AEDs.
- There is high level of evidence eslicarbazepine is associated with overall >50% reduction in seizure frequency (RR 1.86 95% CI 1.46-2.36) over placebo when added on to current therapy for drug-resistant partial epilepsy but patients on eslicarbazepine were more likely to withdraw for adverse events (RR 2.26 95% CI 0.98 to 5.21).
- Maintain eslicarbazepine as non-preferred.

**Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.



A summary of potentially relevant trials are available in **Appendix 2**. Abstracts of these trials are available in **Appendix 3**.

**New Systematic Reviews:**

Efficacy of Antiepileptic Drugs for Secondary Prevention of Seizures after Stroke

A Cochrane Review performed by Sykes, et al.[1] assessed the effects of antiepileptic drugs (AEDs) for the primary and secondary prevention of seizures after stroke. Eligible studies were randomized and quasi-randomized controlled trials in which patients were assigned to treatment or control group (placebo or no drug). Only one trial fulfilled study inclusion criteria: a prospective, randomized, double-blind, placebo-controlled trial comparing valproic acid to placebo for primary prevention of seizures in 72 adults with spontaneous non-aneurysmal, non-traumatic intracerebral hemorrhage. No statistically significant difference in the primary outcome of seizure occurrence at one year was found between the groups. However, the treatment group had a lower, non-statistically significant incidence of early seizures (less than 14 days after onset of hemorrhage) compared to the placebo group. The valproic acid treatment group also demonstrated a statistically significant benefit in the secondary outcome of National Institutes of Health Stroke Scale (NIHSS) score at one year compared to the placebo group. This supports the hypothesis of a neuroprotective/neuro-remodeling effect of valproic acid. Whether these results can be translated to apply to other forms of stroke (e.g. ischemic, subarachnoid hemorrhage) is not certain. There is insufficient evidence to support the routine use of AEDs for the primary and secondary prevention of seizures after stroke.[1]

Immediate-release vs. Controlled-release Carbamazepine formulations

A Cochrane Review performed by Powell, et al.[2] assessed the efficacy of immediate-release carbamazepine (IR CBZ) versus controlled-release carbamazepine (CR CBZ) in patients diagnosed with epilepsy. Eligible studies were RCTs comparing IR CBZ to CR CBZ in patients initiating monotherapy and patients treated with IR CBZ but experiencing unacceptable adverse events. Primary outcomes measured included seizure frequency, incidence of adverse events, proportion with treatment failure and quality of life measures. Ten trials were identified: one trial included patients with newly diagnosed epilepsy and nine trials included patients on treatment with IR CBZ. Eight trials assessing seizure frequency had conflicting results with heterogeneous measures; and only one trial reported a statistically significant reduction in seizures with CR CBZ relative to IR CBZ. Nine trials reported measures of adverse events. There was a trend in favor of CR CBZ with four trials showing statistically significant reduction in adverse events compared to IR CBZ. Two trials reported fewer adverse events with CR CBZ but the difference was not significant. One trial found no difference, and one trial reported more adverse events with CR CBZ but the difference was not significant. There is insufficient evidence to support using CR CBZ over IR CBZ for preventing seizures; however, CR CBZ may be associated with fewer adverse events when compared to IR CBZ and may be an acceptable alternative to patients who are experiencing unacceptable adverse effects from IR CBZ but otherwise have adequate seizure control.[2] The included trials were of small size, poor methodological quality and at high risk of bias, limiting the validity of the conclusions found in the review.

Efficacy of Antiepileptic Drugs as Add-on Therapy

A Cochrane Review performed by Shi, et al.[3] assessed the efficacy and tolerability of felbamate versus placebo when used as an add-on therapy for patients with refractory partial-onset epilepsy. Eligible studies were double-blind, single-blind or open-label randomized placebo-controlled add-on studies of patients of any age with refractory partial-onset seizures. Outcomes measured included 50% or greater reduction in seizure frequency; absolute or percentage reduction in seizure frequency; treatment withdrawal; adverse events; and quality of life. Only three RCTs with a total of 153 subjects were included in the review but due to significant methodological heterogeneity, clinical heterogeneity and differences in outcome measures, a meta-analysis of the results was not possible. None of the studies reported a 50% reduction in seizure frequency and only one study reported absolute and percentage reduction in seizure frequency compared to placebo (34.4 seizures/8 weeks vs. 40.2 seizures/8 weeks, respectively; p=0.046). Adverse effects rates were higher with felbamate than with placebo, particularly headache, nausea and dizziness.[3]



A Cochrane Review performed by Pulman, et al.[4] assessed the effects of tiagabine as add-on treatment in patients with drug-resistant localization-related seizures. Eligible studies were double-blind, single-blind or open-label randomized, placebo or active-controlled add-on trials of patients of any age with localization-related seizures in which an adequate method of concealment of randomization was used. Outcomes measured included 50% or greater reduction in seizure frequency; treatment withdrawal during the study period; adverse effects, cognitive effects; quality of life. Four parallel-group and two cross-over group trials were included. The overall risk ratio (RR) for a 50% or greater reduction in seizure frequency (tiagabine vs. placebo) was 3.16 (95% CI, 1.97 to 5.07) but because of differences in response rates among trials, regression models were unable to provide reliable estimates of response to individual doses. The RR for treatment withdrawal was 1.81 for tiagabine (95% CI, 1.25 to 2.62). Tiagabine was associated with a significant increase in dizziness, fatigue, nervousness and tremor but without difference in cognition or quality of life outcomes.[4]

A second Cochrane Review performed by Pulman, at al.[5] assessed the efficacy and tolerability of pregabalin when used as add-on therapy for drug-resistant partial epilepsy. Eligible studies were RCTs comparing pregabalin with placebo or an alternative AED in patients with drug-resistant partial epilepsy. Outcomes measured included 50% or greater reduction in seizure frequency; seizure freedom (defined as absolute cessation of seizure activity during the study period); treatment withdrawal for any reason during the study period; treatment withdrawal for adverse events; and nature of adverse events. Six industry-sponsored

(n=2009) placebo-controlled studies of short duration (12 weeks) were identified and included in the analysis. Doses of pregabalin studied ranged from 50 mg per day to 600 mg per day. The overall RR for a 50% or greater reduction in seizure frequency (pregabalin vs. placebo) was 2.61 (95% CI, 1.70 to 4.01) with efficacy demonstrated at doses ranging from 150 mg per day to 600 mg per day and odds of response doubling from 300 mg per day to 600 mg per day (OR 2.12; 95% CI, 1.76 to 2.54). Pregabalin was also associated with complete cessation of seizure activity during the study period (RR 2.59; 95% CI, 1.05 to 6.36). Patients were significantly more likely to have withdrawn treatment for any reason with pregabalin than placebo (RR 1.39; 95% CI, 1.13 to 1.72) or for adverse effects (RR 2.69; 95% CI, 1.88 to 3.86). Ataxia, dizziness, somnolence and weight gain were all significantly associated with use of pregabalin. The authors rated the risk of bias as low or unclear due to possibility of publication bias.[5]

A third Cochrane Review performed by Pulman, et al.[6] assessed the efficacy and tolerability of topiramate when used as add-on therapy for patients with drug-resistant partial epilepsy. Eligible studies were RCTs comparing topiramate with placebo or an alternative AED in patients with drug-resistant partial epilepsy. Outcomes measured included 50% or greater reduction in seizure frequency; seizure freedom (defined as absolute cessation of seizure activity during the study period); treatment withdrawal for any reason during the study period; and adverse events. Eleven trials (n=1401) were included, with double-blind phases ranging from 11 to 19 weeks. The overall RR for a 50% or greater reduction in seizure frequency (topiramate vs. placebo) was 2.97 (95% CI, 2.38 to 3.72) with an increasing effect at higher doses, though without any advantage at doses over 300 mg per day. Topiramate was also associated with complete cessation of seizure activity during the study period (RR 3.41; 95% CI, 1.37 to 8.51). Patients were significantly more likely to have withdrawn treatment for any reason with topiramate than placebo (RR 2.44; 95% CI, 1.64 to 3.62). Difficulty concentrating, dizziness, fatigue, paresthesia, somnolence, 'thinking abnormally' and weight loss were all significantly associated with use of topiramate. Evidence of publication bias was found and risk of bias was rated as low or unclear.[6]

**New Guidelines:**
None.



**New FDA Drug Approvals:**
None.

**New Formulations/Indications:**
Rufinamide (BANZEL) received an expanded indication from the FDA in February 2015 for adjunctive treatment of seizures associated with Lennox Gastaut Syndrome in children 1 year of age and older and adults. Previously, the indication was for children 4 years of age and older and adults. Approval was based on a single open-label, active-controlled (rufinamide 45 mg/kg/day (n=25) vs. adjunctive AED of investigator's choice (n=11)), randomized, pharmacokinetic bridging study. The pharmacokinetic profile of rufinamide was not significantly affected by age either as a continuous covariate (1 to 35 years) or a categorical covariate (age categories: 1 to less than 4 years and 4 years of age and older), after body weight was taken into consideration. The adverse reaction profile observed in the rufinamide-treated patients occurred at a rate similar as in earlier trials of children 4 years of age and older and adults. Adverse reactions that occurred in at least 2 patients (8%) treated with rufinamide with higher frequency than the comparator group were: vomiting (24%), somnolence (16%), bronchitis (12%), constipation (12%), cough (12%), decreased appetite (12%), rash (12%), otitis media (8%), pneumonia (8%), decreased weight (8%), gastroenteritis (8%), nasal congestion (8%) and pneumonia aspiration (8%).[7]

**New FDA Safety Alerts:**

Valproate

In January 2015, WARNINGS AND PRECAUTIONS labeling for valproate received new information[8]:

> Birth defects [BLACK BOXED WARNING]: valproate is associated with possible neural tube defects and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations, hypospadias, limb malformations) when used during pregnancy.
>
> Bleeding and other hematopoietic disorders: valproate is associated with dose-related thrombocytopenia. Valproate use has also been associated with decreases in other cell lines and myelodysplasia. Because of reports of cytopenias, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters (e.g., low fibrinogen, coagulation factor deficiencies, acquired von Willebrand's disease), measurements of complete blood counts and coagulation tests are recommended before initiating therapy and at periodic intervals.
>
> Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity reaction: DRESS has been reported in patients taking valproate and may be fatal or life-threatening.

**References:**


1. Sykes L, Wood E, Kwan J. Antiepileptic drugs for the primary and secondary prevention of seizures after stroke. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD005398. DOI: 10.1002/14651858.CD005398.pub3.

2. Powell G, SaundersM,Marson AG. Immediate-release versus controlled-release carbamazepine in the treatment of epilepsy. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD007124. DOI: 10.1002/14651858.CD007124.pub3.

3. Shi LL, Dong J, NiH, Geng J,Wu T. Felbamate as an add-on therapy for refractory epilepsy. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD008295. DOI: 10.1002/14651858.CD008295.pub3.

4. Pulman J, Hutton JL, Marson AG. Tiagabine add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD001908. DOI: 10.1002/14651858.CD001908.pub3.

5. Pulman J, Hemming K, Marson AG. Pregabalin add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD005612. DOI: 10.1002/14651858.CD005612.pub3.

6. Pulman J, Jette N, Dykeman J, Hemming K, Hutton JL,Marson AG. Topiramate add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD001417. DOI: 10.1002/14651858.CD001417.pub3.

7. Banzel (rufinamide) [product information]. Woodcliff Lake, NJ: Eisai Inc., February 2015.

8. Center for Drug Evaluation and Research Webpage. Food and Drug Administration. http://www.fda.gov/Drugs/default.htm. Accessed February 13, 2015.

**Appendix 1:** Current Status on Preferred Drug List

| Preferred | | Non-Preferred | |
|---|---|---|---|
| **GENERIC NAME** | **FORM** | **GENERIC NAME** | **FORM** |
| CARBAMAZEPINE | ORAL SUSP | CARBAMAZEPINE | CPMP 12 HR |
| CARBAMAZEPINE | TAB CHEW | CLOBAZAM | ORAL SUSP |
| CARBAMAZEPINE | TAB ER 12H | CLOBAZAM | TABLET |
| CARBAMAZEPINE | TABLET | DIAZEPAM | RECTAL KIT |
| DIAZEPAM | RECTAL KIT | EZOGABINE | TABLET |
| DIVALPROEX | CAP SPRINK | ESLICARBAZEPINE | TABLET |
| DIVALPROEX | TAB ER 24H | EZOGABINE | TABLET |
| DIVALPROEX | TAB DR | FELBAMATE | ORAL SUSP |
| ETHOSUXIMIDE | CAPSULE | FELBAMATE | TABLET |
| ETHOSUXIMIDE | SOLUTION | GABAPENTIN | SOLUTION |
| ETHOTOIN | TABLET | GABAPENTIN | TABLET |
| GABAPENTIN | CAPSULE | LACOSAMIDE | SOLUTION |
| LACOSAMIDE | TABLET | LAMOTRIGINE | TAB ER 24H |
| LAMOTRIGINE | TABLET | LAMOTRIGINE | TAB RAPIDIS |
| LEVETIRACETAM | SOLUTION | LAMOTRIGINE | TB CHW DSP |
| LEVETIRACETAM | TABLET | LAMOTRIGINE | TB ER DSPK |
| METHSUXIMIDE | CAPSULE | LAMOTRIGINE | TB RD DSPK |
| OXCARBAZEPINE | ORAL SUSP | LEVETIRACETAM | TAB ER 24H |
| OXCARBAZEPINE | TABLET | OXCARBAZEPINE | TAB ER 24H |
| PHENOBARBITAL | ELIXIR | PERAMPANEL | TABLET |
| PHENOBARBITAL | TABLET | PREGABALIN | CAPSULE |
| PHENYTOIN | ORAL SUSP | PREGABALIN | SOLUTION |
| PHENYTOIN | TAB CHEW | RUFINAMIDE | ORAL SUSP |
| PHENYTOIN EXTENDED | CAPSULE | TOPIRAMATE | CAP ER 24H |
| PRIMIDONE | TABLET | TOPIRAMATE | CAP SPRINK |
| RUFINAMIDE | TABLET | VALPROIC ACID | CAPSULE DR |
| TIAGABINE | TABLET | VIGABATRIN | POWD PACK |
| TOPIRAMATE | TABLET | VIGABATRIN | TABLET |
| VALPROIC ACID | CAPSULE | | |
| VALPROIC ACID | SOLUTION | | |
| ZONISAMIDE | CAPSULE | | |

**Appendix 2:** New Clinical Trials

One hundred and five potentially relevant clinical trials were evaluated from the literature search. After further review, 102 trials were not head-to-head RCTs and were therefore excluded. The remaining 3 trials are briefly described in the table below. Full abstracts are included in **Appendix 3**. The Medline search strategy is presented in **Appendix 4**.

**Table 1**: Description of Clinical Trials.

| Study | Comparison | Population | Primary Outcome | Results |
|---|---|---|---|---|
| Rossetti, et al.<br><br>Pragmatic, OL, Phase 2 RCT<br><br>2 sites<br><br>Duration 1 year | • Levetiracetam titrated up to 1500 mg BID<br>vs.<br>• Pregabalin titrated up to 300 mg BID<br>*Flexible dosing* | Adults w/ primary brain tumor (WHO grades II-IV) provoking ≥1 seizure episode. | Composite endpoint of:<br>• Status epilepticus<br>• 2 seizures w/ impaired consciousness<br>• Need of 2nd AED<br>• Need to d/c study drug (lack of effectiveness or adverse events) | • Levetiracetam 36%<br>• Pregabalin 44%<br><br>Note: composite primarily driven by need for 2nd AED with pregabalin users. |
| Baulac, et al.<br><br>MC, DB, RCT<br><br>Extension study of a Phase 3 trial | • Zonisamide 200-500 mg Qday*<br>vs.<br>• Carbamazepine 200-600 mg BID*<br>*Flexible dosing* | Patients who completed Phase 3 trial seizure-free and willing to maintain seizure diary and report AEs | Retention rate, defined as the proportion of patients remaining in the extension study at each visit for tin ITT population. | • Zonisamide 87.6%<br>• Carbamazepine 84.8%<br><br>Note: reason for extension study was to assess tolerability, for which both drugs were tolerated well. Discontinuation due to AE was rare. |
| Zaccara, et al.<br><br>MC, DB, PG, NI, RCT | • Levetiracetam titrated up to 1500 mg BID<br>vs.<br>• Pregabalin titrated up to 300 mg bid<br>*Used as adjunctive therapy w/ flexible dosing* | Adults w/ epilepsy with partial seizures inadequately controlled with 2-4 AEDs other than pregabalin or levetiracetam | Responder rate, defined as proportion of patients w/ ≥50% reduction in 28-day seizure rate (all partial seizures) over 12-week maintenance phase, as compared with baseline. | • Levetiracetam 58.8%<br>• Pregabalin 59.1%<br><br>Note: Lower bound of 95% CI was -8.0%, which was greater than the pre-specified noninferiority margin of -12.0%. Thus, pregabalin was noninferior to levetiracetam. |

Abbreviations: AE = adverse event; AED = antiepileptic drug; CI = confidence interval; DB = double blind; ITT = intention to treat; MC = multi-centered; NI = non-inferiority design; OL = open label; PG = parallel group; RCT = randomized controlled trial; WHO = World Health Organization.

**Appendix 3:** Abstracts of Clinical Trials

**Rossetti A, Jeckelmann S, Novy J, et al. Levetiracetam and pregabalin for antiepileptic monotherapy in patients with primary brain tumors. A phase II randomized study. *Neuro-Oncology*. 2014;16:584-588.**

Background. In patients with brain tumors, the choice of antiepileptic medication is guided by tolerability and pharmacokinetic interactions. This study investigated the effectiveness of levetiracetam (LEV) and pregabalin (PGB), 2 non-enzyme-inducing agents, in this setting.
Methods. In this pragmatic, randomized, unblinded phase II trial (NCT00629889), patients with primary brain tumors and epilepsy were titrated to a monotherapy of LEV or PGB. Efficacy and tolerability were assessed using structured questionnaires. The primary composite endpoint was the need to discontinue the study drug, add-on of a further antiepileptic treatment, or occurrence of at least 2 seizures with impaired consciousness during 1 year follow-up.
Results. Over 40 months, 25 patients were randomized to LEV, and 27 to PGB. Most were middle-aged men, with a high-grade tumor and at least one generalized convulsion. Mean daily doses were 1125 mg (LEV) and 294 mg(PGB). Retention rates were 59% in the LEV group, and 41%in the PGB group. The composite endpoint was reached in 9 LEV and 12 PGB patients—need to discontinue: side effects, 6 LEV, 3 PGB; lack of efficacy, 1 and 2; impaired oral administration, 0 and 2; add-on of another agent: 1 LEV, 4 PGB; and seizures impairing consciousness: 1 in each. Seven LEV and 5 PGB subjects died of tumor progression.
Conclusions. This study shows that LEV and PGB represent valuable monotherapy options in this setting, with very good antiepileptic efficacy and an acceptable tolerability profile, and provides important data for the design of a phase III trial.

**Baulac M, Patten A, Giorgi L. Long-term safety and efficacy of zonisamide versus carbamazepine monotherapy for treatment of partial seizures in adults with newly diagnosed epilepsy: results of a phase III, randomized, double-blind study. *Epilepsia*. 2014;55:1534-1543.**



Objective: To investigate the long-term safety and maintenance of efficacy of monotherapy with once-daily zonisamide versus twice-daily controlled-release carbamazepine for partial seizures in adults with newly diagnosed epilepsy.
Methods: Long-term, double-blind, extension study, conducted in patients completing a phase III noninferiority trial comparing zonisamide and carbamazepine monotherapy. Patients continued their randomized treatment, with dosing adjusted according to tolerability/response (zonisamide 200–500 mg/day; carbamazepine 400–1,200 mg/day). Safety assessments included treatment-emergent adverse events (TEAEs) and clinical laboratory parameters. Efficacy assessments included retention rate and the proportion of patients remaining seizure free for ≥24 months.
Results: Overall, 120 (87.6%) of 137 patients randomized to zonisamide and 134 (84.8%) of 158 patients randomized to carbamazepine completed the study. More than three-fourths of patients were exposed to >24 months of treatment. For zonisamide versus carbamazepine, incidences were similar for TEAEs (52.6% vs. 46.2%), serious treatment-related TEAEs (0.7% vs. 1.9%), and TEAEs leading to withdrawal (1.5% vs. 0.6%). The incidence of treatment-related TEAEs was 26.3% for zonisamide compared with 19.6% for carbamazepine, and the most frequently reported treatment-related TEAEs were decreased weight (5.1% vs. 0%), decreased appetite (3.6% vs. 0%), memory impairment (2.9% vs. 3.2%), and decreased hemoglobin level (1.5% vs. 3.2%). Most TEAEs were of mild or moderate intensity. There were no reports of Stevens-Johnson syndrome or toxic epidermal necrolysis in either group. Zonisamide was associated with small-to-moderate decreases in bicarbonate levels from baseline (mean 3.4 mM). There were no reports of metabolic acidosis. Retention rates were generally similar between treatment groups at all time points throughout the extension study. The proportion of patients remaining seizure free for ≥24 months was also similar for zonisamide (32.3%) and carbamazepine (35.2%).
Significance: Once-daily zonisamide monotherapy demonstrated favorable long-term safety and maintenance of efficacy in treating partial seizures in adults with newly diagnosed epilepsy. No new or unexpected safety findings emerged.

**Zaccara G, Almas M, Pitman V, et al. Efficacy and safety of pregabalin versus levetiracetam as adjunctive therapy in patients with partial seizures: a randomized, double-blind, noninferiority trial. *Epilepsia*. 2014;55:1048-1057.**

Objectives: To assess the comparative efficacy and safety of pregabalin and levetiracetam for the reduction of seizure frequency in patients with partial seizures.
Methods: This was a randomized, double-blind, flexible-dose, parallel-group noninferiority study of pregabalin and levetiracetam (randomized 1:1) as adjunctive treatment in adult patients with refractory partial seizures. The study included a 6-week baseline phase, 4-week dose-escalation phase, and 12-week maintenance phase. The primary endpoint was the proportion of patients with a ≥50% reduction in 28-day seizure rate during the 12-week maintenance phase, as compared with baseline. Noninferiority of pregabalin was declared if the lower limit of the 95% confidence interval (CI) for the difference in responder rates was greater than the prespecified noninferiority margin of 12%. A key secondary endpoint was the percent change from baseline in 28-day seizure rate during the dose-escalation and maintenance phases.
Results: Five hundred nine patients were randomized to pregabalin (n = 254) or levetiracetam (n = 255) and 418 (208 pregabalin, 210 levetiracetam) completed the maintenance phase. With both pregabalin and levetiracetam, the proportion of patients with a ≥50% reduction in 28-day seizure rate was 0.59 (difference between groups, 0.00 [95% CI, -0.08 to 0.09]). Because the lower bound of the 95% CI was greater than the prespecified noninferiority margin of 12%, pregabalin was not inferior to levetiracetam. There was no significant difference between pregabalin and levetiracetam in the percent change in 28-day seizure rate (median difference, 4.1 [95% CI,2.6 to 10.9], p = 0.3571). In a post hoc analysis, the proportion of patients who were seizure-free for the maintenance phase was lower with pregabalin (8.4%) than with levetiracetam (16.2%), p = 0.0155. Safety profiles were similar and consistent with prior trials.
Significance: These results indicate that pregabalin is noninferior, and has a similar tolerability, to levetiracetam as adjunctive therapy in reducing seizure frequency in patients with partial seizures.

**Appendix 4:** Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to February Week 2 2015

1 exp Epilepsy, Partial, Motor/ or exp Epilepsy, Temporal Lobe/ or exp Epilepsy, Complex Partial/ or exp Epilepsy, Partial, Sensory/ or exp Epilepsy, Reflex/ or exp Epilepsy, Benign Neonatal/ or exp Epilepsy, Tonic-Clonic/ or exp Epilepsy, Post-Traumatic/ or exp Epilepsy, Absence/ or exp Epilepsy, Frontal Lobe/ or exp Epilepsy/ or exp Epilepsy, Rolandic/ or exp Myoclonic Epilepsy, Juvenile/ or exp Epilepsy, Generalized/ 69190
2 exp Seizures/ 20691
3 1 or 2 69371
4 exp Carbamazepine/ 4987
5 exp Diazepam/ 4190
6 exp Valproic Acid/ 6627
7 exp Ethosuximide/ 245
8 ethotoin.mp. 2
9 gabapentin.mp. 4122
10 lacosamide.mp. 333
11 lamotrigine.mp.3660
12 levetiracetam.mp. 1812
13 methsuximide.mp. 17
14 oxcarbazepine.mp. 1218
15 exp Phenobarbital/ 2849
16 exp Phenytoin/ 2907
17 clobazam.mp. 335
18 ezogabine.mp. 228
19 ESLICARBAZEPINE.mp. 113
20 felbamate.mp. 455
21 perampanel.mp. 76
22 pregabalin.mp. 1663
23 rufinamide.mp. 136
24 topiramate.mp. 3233
25 exp Vigabatrin/ 952
26 exp Anticonvulsants/ 48264
27 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 53710
28 3 and 27 18433
29 limit 28 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or pragmatic clinical trial or randomized controlled trial or systematic reviews) 3963
30 limit 29 to (english language and yr="2014 -Current") 105



Author: A. Gibler, Pharm.D. Date: March 2015

# Clobazam (Onfi®)

**Goal(s):**

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

**Length of Authorization:**

- 12 months

**Requires PA:**

- Non-preferred drugs
- Clobazam (Onfi®)

**Covered Alternatives:**

Preferred alternatives listed at www.orpdl.org

| Approval Criteria | | |
|---|---|---|
| 1. What diagnosis is being treated? | Record ICD9 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 Action:* *3/15; 5/12 (MH)*
*Revision(s):*
*Initiated:* *8/20/12*

# Topiramate

**Goal(s):**

- Approve topiramate only for covered diagnoses (above the line) which are supported by the medical literature (e.g. epilepsy, and migraine prophylaxis).

**Length of Authorization:**

90 days to lifetime

**Requires PA:**

- Non-preferred topiramate products

**Covered Alternatives:**

- Preferred alternatives listed at www.orpdl.org

| Approval Criteria | | |
|---|---|---|
| 1. What diagnosis is being treated? | Record ICD9 code. | |
| 2. Does the patient have a diagnosis of epilepsy (ICD-9 code 345.0-345.9, 780.39, or 907.0)? | Yes: Approve for lifetime (until 12-31-2036) | No: Go to #3 |
| 3. Does the patient have a diagnosis of migraine (ICD-9 346)? | Yes: Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime* | No: Go to #4 |
| 4. Does the client have a diagnosis of bipolar affective disorder or schizoaffective disorder?<br>• ICD-9 296 and subsets<br>• ICD-9 295 and subsets | Yes: Go to #5 | No: Go to #6 |



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| Approval Criteria | | |
|---|---|---|
| 5. Has the client tried or are they contraindicated to at least two of the following drugs:<br>• Lithium<br>• Valproate and derivatives<br>• Lamotrigine<br>• Carbamazepine<br>• Atypical antipsychotic<br><br>Document drugs tried or contraindications. | Yes: Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.* | No: Pass to RPH; Deny, (Medical Appropriateness) and recommend trial of covered alternative. |
| 6. Is the client using the medication for weight loss? (Obesity ICD9 278.0, 278.01)? | Yes: Pass to RPH; Deny, (Not covered by the OHP) | No: Go to #7. |
| 7. Pass to RPH.<br><br>All other indications need to be evaluated for appropriateness:<br><br>• Neuropathic pain<br>• Post-Traumatic Stress Disorder (PTSD)<br>• Substance abuse | Use is off-label: Deny, (Medical Appropriateness), other treatments should be tried as appropriate.<br><br>Below the line diagnoses: Deny (Not covered by the OHP)<br><br>If clinically warranted: Deny, yesterday's date (Medical Appropriateness) and use clinical judgment to approve for 1 month starting today to allow time for appeal.<br><br>MESSAGE: "Although the request has been denied for long term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal." | |



*P&T / DUR Action:* *3/15, 2/12, 9/07, 11/07*
*Revision(s):* *5/12, 1/12*
*Initiated:* *1/11*