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Literature Scan: Antiepileptics

Date of Review: March 2018

Date of Last Review: July 2016
End Date of Literature Search: 12/11/2017

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

Conclusions:

- There are no new evidence-based guidelines of antiepileptic drugs (AEDs) identified on which to recommend changes to the PDL class.
- Two Cochrane reviews included moderate to high quality evidence to evaluate carbamazepine safety and efficacy compared with lamotrigine or topiramate when used as monotherapy in patients with epilepsy.[1,2] Lamotrigine was significantly less likely to be withdrawn than carbamazepine, but the results for time to first seizure suggested that carbamazepine may be superior in terms of seizure control.[1] For individuals with focal onset seizures, there is evidence that 12-month remission will be achieved earlier with carbamazepine than with topiramate.[2]
- A systematic review evaluating the safety of levetiracetam in pediatric patients identified behavioral problems and somnolence as the most prevalent adverse events and the most common causes of treatment discontinuation.[4] In addition, children receiving levetiracetam in combination with other AEDs had a greater risk of adverse events than those receiving monotherapy with levetiracetam.[4]
- Five AED medications received expanded indications from the Food and Drug Administration (FDA) since the last AED class update. Fosphenytoin received approval for use in pediatric patients with status epilepticus from birth through 17 years of age.[5] Lacosamide and eslicarbazepine are now indicated for use in pediatric patients with focal onset seizures aged 4 years and older.[6,7] Only the oral formulations of lacosamide are approved for use in children; the intravenous (IV) product remains recommended for use only in adults.[6] Perampanel received an expanded indication for monotherapy for treatment of focal seizures with or without secondary generalized seizures in patients with epilepsy 12 years of age and older.[8] Brivaracetam received an expanded indication for monotherapy treatment in patients with focal seizures in patients 16 years of age and older with epilepsy.[9]
- The FDA expanded safety warnings for 4 AEDs since the last class update. The warnings and precaution labeling for perampanel and lacosamide were revised to include information about Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, associated with therapy.[6,8] DRESS may be fatal or life-threatening and patients should be evaluated immediately if they experience fever, rash, lymphadenopathy, and/or facial swelling. Labeling for levetiracetam was updated to include warnings and precautions describing the risk for anaphylaxis and angioedema associated with levetiracetam administration.[10] Measurement of serum sodium and chloride levels should be considered during maintenance treatment with eslicarbazepine, particularly if the patient is receiving other medications known to decrease serum sodium levels, and should be performed if symptoms of hyponatremia develop.[7]

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Recommendations:

- No further review or research needed at this time. After reviewing comparative drug costs in the executive session, no PDL changes were recommended.

Previous Conclusions:

- The American Academy of Neurology and the American Epilepsy Society published evidence-based guidelines for starting AEDs in adults after a first seizure. The authors found moderate evidence that immediate AED therapy as compared with no treatment is likely to reduce absolute risk by about 35% for a seizure recurrence within the subsequent 2 years.
- There is moderate quality evidence lacosamide is effective and well tolerated in the short term when used as add-on treatment for drug-resistant partial epilepsy in adults.
- There are insufficient data to address the risk-benefit balance of vigabatrin versus carbamazepine monotherapy for epilepsy in adults and children.
- There is moderate quality evidence that describes common adverse effects with lamotrigine therapy in pediatric patients. The most commonly reported adverse events include: rash, headache, fever, somnolence, vomiting, seizure aggravation, dizziness, cough, aggression, ataxia and insomnia. Children on lamotrigine monotherapy had lower incidences of adverse events compared to those taking multiple AEDs.
- There is low quality evidence that levetiracetam is effective in reducing neuropathic pain but it is associated with an increase in adverse events and premature discontinuation due to side effects.
- There is moderate quality evidence that discontinuing an AED in children prior to at least 2 seizure-free years is associated with a higher recurrence rate than waiting 2 or more seizure-free years. The optimal time of withdrawal is not clear due to insufficient evidence. There is no evidence to guide AED discontinuation in adults.
- For all the currently marketed AEDs, there is no evidence to support the use of any of them in treating migraines. Topiramate, sodium valproate and divalproex are effective prophylactic treatments for episodic migraine in adults. There is insufficient evidence to further support the use of gabapentin in migraine prophylaxis.
- There is low quality evidence that topiramate may be effective in reducing the frequency of binge eating in patients with binge-eating disorder

Previous Recommendations:

- No further review or research needed at this time. After the executive session, no changes to the PDL were made.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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 drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice 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.

New Systematic Reviews:

Cochrane: Individual Participant Data Reviews

A series of Cochrane reviews evaluating pair-wise monotherapy comparisons of carbamazepine, phenobarbital, lamotrigine, topiramate, phenytoin and valproate were updated in 2016 and 2017.[1,2,11-13] Each of these updates compiled a meta-analysis of individual participant data (IPD), in which the raw individual level data for each study were obtained from the investigators and used for synthesis of the meta-analysis.[14] Traditional meta-analysis methods involve combining quantitative evidence from related studies to evaluate outcomes. The goal of IPD meta-analysis is to summarize the raw data on a specific clinical question from multiple related studies.[14] IPD analyses are time consuming to generate because the original investigators must be contacted to ask if they will share their raw data for the report. Only the updates that were based on moderate to high quality evidence will be described in detail for this class update. Three separate updates evaluated carbamazepine and phenobarbital, [11] carbamazepine and phenytoin,[13] and phenytoin with valproate,[12] but the recently published trials included in these updates were imprecise and may have misclassified seizure type, so the methodological quality of the evidence was rated as low by the Cochrane reviewers. Therefore, they are not included in this summary.

One of the Cochrane updates in this series evaluated new evidence published through October 2017 for head to head trials comparing lamotrigine to carbamazepine in people with focal or generalized onset seizures.[1] The authors used the IPD method to compile data for the meta-analysis. The primary outcome was time to withdrawal of allocated treatment. Secondary outcomes included time to first seizure, time to remission, and incidence of adverse events. Thirteen studies were identified for this update. IPD were available for 2572 participants out of 3394 individuals from 9 out of 13 trials, or 78% of the potential data.[1] The results of this review are applicable mainly to individuals with focal seizures as 88% of included individuals experienced seizures of this type at baseline.[1] The methodological quality of the included trials was generally good, but there is some evidence that the design choice of open-label treatment may have influenced the withdrawal rates of the trials.[1] Therefore, the quality of the evidence for the primary outcome of treatment withdrawal was judged as moderate for individuals with focal seizures and low for individuals with generalized seizures.[1] For efficacy outcomes (first seizure and remission), the quality of evidence was rated as high for individuals with focal seizures and moderate for individuals with generalized seizures.[1] For remission outcomes, a hazard ratio (HR) less than one indicated an advantage for carbamazepine, and for first seizure and withdrawal outcomes a HR less than one indicated an advantage for lamotrigine.[1] Results were pooled and adjusted for seizure type when HR were calculated. The main results showed a significant advantage for lamotrigine compared to carbamazepine for withdrawal but a significant advantage for carbamazepine compared to lamotrigine for first seizure and six-month remission [time to withdrawal of allocated treatment (HR 0.72, 95% CI 0.63 to 0.82); time to first seizure (HR 1.22, 95% CI 1.09 to 1.37); and time to six-month remission (HR 0.84, 95% CI 0.74 to 0.94)].[1] No difference was found between the 2 drugs for time to 12-month remission (HR 0.91, 95% CI 0.77 to 1.07) or time to 24-month remission (HR 1.00, 95% CI 0.80 to 1.25), however, only two trials included follow up for more than one year so the evidence is limited for this outcome.[1] The most commonly reported adverse events for both of the drugs across all of the included trials were dizziness, fatigue, gastrointestinal disturbances, headache and rash. The rate of adverse events was similar for the carbamazepine and lamotrigine.[1] Lamotrigine was significantly less likely to be withdrawn than carbamazepine, but the results for time to first seizure suggested that carbamazepine may be have improved seizure control up to 6 months.[1]

A second pairwise analysis with carbamazepine and topiramate evaluated comparative head to head evidence in patients with focal and generalized seizures through April 2016. The primary outcome was time to withdrawal of allocated treatment, and secondary outcomes were time to first seizure, time to remission, and incidence of adverse events. Three studies were identified and IPD were available for 1151 of 1239 eligible individuals from 2 of the 3 studies, or 93% of the

potential data.[2] Data from the third trial (n=88) was unavailable. A small proportion of individuals recruited into these trials had unclassified seizures so for analysis purposes these individuals were grouped with those with generalized onset seizures.[2] The results of this review are applicable mainly to individuals with focal onset seizures as 85% of included individuals experienced seizures of this type.[2] The methodological quality of the included trials was good; however, there was some evidence that the open label design of the larger of the two trials may have influenced the withdrawal rate from the trial.[2] Therefore, the evidence for the primary outcome of treatment withdrawal was rated as moderate for individuals with focal seizures and low for individuals with generalized seizures.[2] For efficacy outcomes (first seizure and remission), the authors judged the evidence from this review to be high quality for individuals with focal seizures and moderate quality for individuals with generalized or unclassified seizures.[2] For remission outcomes, a HR less than 1 indicated an advantage for carbamazepine, and for first seizure and withdrawal outcomes, a HR less than 1 indicated an advantage for topiramate.[2] There were no significant differences between carbamazepine and topiramate in time to withdrawal, time to first seizure or 6-month remission rates [time to withdrawal of allocated treatment (HR 1.16, 95% CI 0.98 to 1.38); time to first seizure (HR 1.11, 95% CI 0.96 to 1.29); and time to 6-month remission (HR 0.88, 95% CI 0.76 to 1.01)].[2] However, a trend toward improved remission with carbamazepine was shown for time to 12-month remission (HR 0.84, 95% CI 0.71 to 1.00) compared to topiramate.[2] The most commonly reported adverse events with both drugs were drowsiness or fatigue, tingling sensation, headache, gastrointestinal disturbance and anxiety or depression. The rate of adverse events was similar for topiramate and carbamazepine.[2] For individuals with focal onset seizures, there is evidence that 12-month remission will be achieved earlier with carbamazepine than with topiramate.[2]

Pediatrics

A 2016 systematic review evaluated adverse effects observed in children taking levetiracetam.[4] The literature search was conducted through February 2015. Sixty-seven articles involving 3174 patients ages 18 years or younger were identified. The identified literature included twenty prospective cohort studies, 21 retrospective cohort studies, 4 pharmacokinetic studies, 16 case reports, and 6 RCTs. Five of the 6 RCTs were evaluated as having a low risk of bias. One RCT had a high risk of bias due to uncertain blinding methods for outcome assessments and investigators.[4] A meta-analysis of the RCTs was completed to evaluate the association between levetiracetam and commonly reported adverse effects (AEs) or treatment discontinuation stratified by type of regimen (monotherapy vs. polytherapy). A total of 1,913 AEs were reported across all 67 studies.[4] The most common AEs were behavioral problems and somnolence, which accounted for 10.9% and 8.4% of all AEs in prospective studies.[4] In the prospective studies involving 1120 children, 47% of these children experienced AEs.[4] Significantly more children experienced AEs with polytherapy (64%) than monotherapy (22%) ($p<0.001$).[4]

New Guidelines: No new guidelines were identified since the last literature scan.

New Formulations or Indications:

Cerebyx® (fosphenytoin) (March 2017): Fosphenytoin received expanded approval for pediatric patients from birth to less than 17 years of age for the treatment of generalized status epilepticus.[5] Prior to this approval, fosphenytoin was not labeled for administration in pediatric patients. Pediatric dosing is different from adult dosing in that loading doses should be administered in the range of 10 to 15 mg phenytoin equivalents (PE) per kilogram (kg) followed by a maintenance dose of 2 to 4 mg PE/kg every 12 hours.[5] The recommended adult loading dose is 15 to 20 mg PE/kg followed by a maintenance dose of 4 to 6 mg PE/kg in divided doses.[5]

Fycompa® (perampanel) (July 2017): Perampanel received an expanded indication for monotherapy for treatment of focal seizures with or without secondary generalized seizures in patients with epilepsy 12 years of age and older.[8] The pediatric approval was based on FDA guidance that permits drug efficacy in adults to be extrapolated to pediatric patients.[15] Only efficacy data may be extrapolated; safety studies must still be conducted in pediatric populations. The original

FDA approved indication for perampanel in 2012 was as adjunctive therapy for treatment of focal seizures with or without secondarily generalized seizures in patients aged 12 years and older.

Briviact® (brivaracetam) (September 2017): Brivaracetam received an expanded indication for monotherapy treatment in patients with focal seizures in patients 16 years of age and older with epilepsy as of September 2017.[9] Brivaracetem was originally FDA approved in 2016 as adjunctive treatment for focal seizures in patients 16 years of age and older with epilepsy.

Aptiom® (eslicarbazepine) (September 2017): Eslicarbazepine received FDA approval for management of focal seizures in pediatric patients age 4 years or older.[7] The original approval of eslicarbazepine in 2013 was only in adults with focal seizures. Approval for use in children was based on FDA guidance that permits extrapolation of data to support pediatric use. Data from 3 clinical trials support the safety and tolerability of eslicarbazepine in children.[16]

Vimpat® (lacosamide) (November 2017): Lacosamide tablets and oral solution are now approved in pediatric patients aged 4 to 17 years.[6] The original FDA approval was only in adults with focal seizures. The injectable formulation continues to be only approved for use in adults aged 17 years and older.[6]

New FDA Safety Alerts:

Fycompa® (perampanel) (July 2017): The warnings and precautions labeling for perampanel was revised to include information about Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking perampanel.[8] DRESS may be fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection.[8] Eosinophilia is often present. If such signs or symptoms are present, the patient should be evaluated immediately. Perampanel should be discontinued if an alternative etiology for the signs or symptoms cannot be established.[8]

Vimpat® (lacosamide) (March 2017): Lacosamide warnings and precautions section was updated to include the risk of DRESS, a very serious adverse drug event which has been reported with other AEDs.[6]

Keppra® (levetiracetam) (April 2017): Labeling for levetiracetam updated to include warnings and precautions describing the risk for anaphylaxis and angioedema associated with levetiracetam administration.[10]

Aptiom® (eslicarbazepine) (September 2017): Clinically significant hyponatremia (sodium less than 125 mEq/L) can develop in patients taking eslicarbazepine. Measurement of serum sodium and chloride levels should be considered during maintenance treatment with eslicarbazepine, particularly if the patient is receiving other medications known to decrease serum sodium levels, and should be performed if symptoms of hyponatremia develop (e.g., nausea/vomiting, malaise, headache, lethargy, confusion, irritability, muscle weakness/spasms, obtundation, or increase in seizure frequency or severity).[7] Cases of symptomatic hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported during postmarketing use. In clinical trials, patients whose treatment with eslicarbazepine was discontinued because of hyponatremia generally experienced normalization of serum sodium within a few days without additional treatment.[7]

Randomized Controlled Trials:

A total of 138 citations were manually reviewed from the initial literature search. After further review, 137 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Baulac, et al[17]	Lacosamide titrated up to 600 mg/day via protocol vs. carbamazepine CR titrated up to 1200 mg/day via protocol Phase 3, RCT, DB, MC non-inferiority trial	Patients aged 16 years or greater with focal or generalized seizures N= 888	Proportion of patients who remained seizure free for 6 months after dose stabilization. The predefined non-inferiority criteria was lower limit of 95% CI of absolute difference greater than -12%	Proportion of patients with seizures after 6 months of treatment. Full analysis set: Lacosamide 89.8% (n=444) Carbamazepine CR 91.1% (n=442) Absolute treatment-difference: −1.3%, 95% CI −5.5 to 2.8 Per protocol set: Lacosamide 91.5% (n=408) Carbamazepine CR 92.8% (n=397) Absolute treatment-difference: −1.3%, 95% CI −5.3 to 2.7

Abbreviations: CI = Confidence Interval; CR = controlled release; DB = double blind; MC = multi center; RCT = randomized controlled trial

References:

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3. Chang X-C, Yuan H, Wang Y, Xu H-Q, Hong W-K, Zheng R-Y. Eslicarbazepine acetate add-on for drug-resistant partial epilepsy. *Cochrane Database Syst Rev.* 2017(10).
4. Egunsola O, Choonara I, Sammons HM. Safety of Levetiracetam in Paediatrics: A Systematic Review. *PLoS ONE.* 2016;11(3):e0149686.
5. Cerebyx® (Fosphenytoin) Prescribing Information. New York, NY; Pfizer, Inc.: March 2017.
6. Vimpat® (lacosamide) Prescribing Information. Smyrna, GA; UCB, Inc.: November 2017.
7. Collier DH, Bitman B, Coles A, Liu L, Kumar S, Judd C. A novel electromechanical autoinjector, AutoTouchTM, for self-injection of etanercept: real-world use and benefits. *Postgrad Med.* 2017;129(1):118-125.
8. Fycompa® (perampanel) Product Information. Woodcliff Lake, NJ: Eisai, Inc; July 2017.
9. Briviact® (brivaraceteam) Prescribing Information. Smyrna, GA: UCB, Inc.; September 2017.
10. Keppra® (levetiracetem) Prescribing Information. Smyrna, GA; UCB, Inc.: October, 2017.
11. Nolan SJ, Marson AG, Weston J, Tudur Smith C. Carbamazepine versus phenobarbitone monotherapy for epilepsy: an individual participant data review. *Cochrane Database Syst Rev.* 2016;12:CD001904.
12. Nolan SJ, Marson AG, Weston J, Tudur Smith C. Phenytoin versus valproate monotherapy for partial onset seizures and generalised onset tonic-clonic seizures: an individual participant data review. *Cochrane Database Syst Rev.* 2016;4:CD001769.
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14. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *Bmj.* 2010;340.
15. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs. *Pediatrics.* 2011.
16. Food and Drug Administration. Eslicarbazepine Supplement Approval Letter. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/022416Orig1s009ltr.pdf. Accessed January 8, 2018.
17. Baulac M, Rosenow F, Toledo M, et al. Efficacy, safety, and tolerability of lacosamide monotherapy versus controlled-release carbamazepine in patients with newly diagnosed epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. *Lancet Neurology.* 2017;16(1):43-54.

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
PHENOBARBITAL	PHENOBARBITAL	ORAL	ELIXIR	Y
PHENOBARBITAL	PHENOBARBITAL	ORAL	TABLET	Y
DIAZEPAM	DIASTAT	RECTAL	KIT	Y
DIAZEPAM	DIASTAT ACUDIAL	RECTAL	KIT	Y
PHENYTOIN SODIUM EXTENDED	DILANTIN	ORAL	CAPSULE	Y
PHENYTOIN SODIUM EXTENDED	PHENYTOIN SODIUM EXTENDED	ORAL	CAPSULE	Y
PHENYTOIN SODIUM EXTENDED	PHENYTEK	ORAL	CAPSULE	Y
PHENYTOIN	DILANTIN-125	ORAL	ORAL SUSP	Y
PHENYTOIN	PHENYTOIN	ORAL	ORAL SUSP	Y
PHENYTOIN	DILANTIN	ORAL	TAB CHEW	Y
PHENYTOIN	PHENYTOIN	ORAL	TAB CHEW	Y
ETHOTOIN	PEGANONE	ORAL	TABLET	Y
VALPROIC ACID (AS SODIUM SALT)	DEPAKENE	ORAL	SOLUTION	Y
VALPROIC ACID (AS SODIUM SALT)	VALPROIC ACID	ORAL	SOLUTION	Y
VALPROIC ACID	DEPAKENE	ORAL	CAPSULE	Y
VALPROIC ACID	VALPROIC ACID	ORAL	CAPSULE	Y
DIVALPROEX SODIUM	DEPAKOTE SPRINKLE	ORAL	CAP DR SPR	Y
DIVALPROEX SODIUM	DIVALPROEX SODIUM	ORAL	CAP DR SPR	Y
DIVALPROEX SODIUM	DEPAKOTE	ORAL	TABLET DR	Y
DIVALPROEX SODIUM	DIVALPROEX SODIUM	ORAL	TABLET DR	Y
DIVALPROEX SODIUM	DIVALPROEX SODIUM	ORAL	TABLET DR	Y
DIVALPROEX SODIUM	DEPAKOTE ER	ORAL	TAB ER 24H	Y
DIVALPROEX SODIUM	DIVALPROEX SODIUM ER	ORAL	TAB ER 24H	Y
PRIMIDONE	MYSOLINE	ORAL	TABLET	Y
PRIMIDONE	PRIMIDONE	ORAL	TABLET	Y
METHSUXIMIDE	CELONTIN	ORAL	CAPSULE	Y
ETHOSUXIMIDE	ETHOSUXIMIDE	ORAL	CAPSULE	Y
ETHOSUXIMIDE	ZARONTIN	ORAL	CAPSULE	Y
ETHOSUXIMIDE	ETHOSUXIMIDE	ORAL	SOLUTION	Y
ETHOSUXIMIDE	ZARONTIN	ORAL	SOLUTION	Y
CARBAMAZEPINE	CARBAMAZEPINE	ORAL	ORAL SUSP	Y
CARBAMAZEPINE	TEGRETOL	ORAL	ORAL SUSP	Y
CARBAMAZEPINE	CARBAMAZEPINE	ORAL	TABLET	Y
CARBAMAZEPINE	EPITOL	ORAL	TABLET	Y
CARBAMAZEPINE	TEGRETOL	ORAL	TABLET	Y
CARBAMAZEPINE	CARBAMAZEPINE	ORAL	TAB CHEW	Y

CARBAMAZEPINE	CARBAMAZEPINE ER	ORAL	TAB ER 12H	Y
CARBAMAZEPINE	TEGRETOL XR	ORAL	TAB ER 12H	Y
LAMOTRIGINE	LAMICTAL	ORAL	TABLET	Y
LAMOTRIGINE	LAMOTRIGINE	ORAL	TABLET	Y
GABAPENTIN	GABAPENTIN	ORAL	CAPSULE	Y
GABAPENTIN	NEURONTIN	ORAL	CAPSULE	Y
GABAPENTIN	GABAPENTIN	ORAL	TABLET	Y
GABAPENTIN	NEURONTIN	ORAL	TABLET	Y
TOPIRAMATE	TOPAMAX	ORAL	TABLET	Y
TOPIRAMATE	TOPIRAMATE	ORAL	TABLET	Y
OXCARBAZEPINE	OXCARBAZEPINE	ORAL	ORAL SUSP	Y
OXCARBAZEPINE	TRILEPTAL	ORAL	ORAL SUSP	Y
OXCARBAZEPINE	OXCARBAZEPINE	ORAL	TABLET	Y
OXCARBAZEPINE	TRILEPTAL	ORAL	TABLET	Y
TIAGABINE HCL	GABITRIL	ORAL	TABLET	Y
TIAGABINE HCL	TIAGABINE HCL	ORAL	TABLET	Y
LEVETIRACETAM	KEPPRA	ORAL	TABLET	Y
LEVETIRACETAM	LEVETIRACETAM	ORAL	TABLET	Y
LEVETIRACETAM	ROWEEPRA	ORAL	TABLET	Y
LEVETIRACETAM	KEPPRA	ORAL	SOLUTION	Y
LEVETIRACETAM	LEVETIRACETAM	ORAL	SOLUTION	Y
ZONISAMIDE	ZONEGRAN	ORAL	CAPSULE	Y
ZONISAMIDE	ZONISAMIDE	ORAL	CAPSULE	Y
RUFINAMIDE	BANZEL	ORAL	TABLET	Y
LACOSAMIDE	VIMPAT	ORAL	TABLET	Y
LAMOTRIGINE	LAMICTAL	ORAL	TB CHW DSP	V
LAMOTRIGINE	LAMOTRIGINE	ORAL	TB CHW DSP	V
LAMOTRIGINE	LAMICTAL (BLUE)	ORAL	TAB DS PK	V
LAMOTRIGINE	LAMICTAL (GREEN)	ORAL	TAB DS PK	V
LAMOTRIGINE	LAMICTAL (ORANGE)	ORAL	TAB DS PK	V
LAMOTRIGINE	LAMICTAL ODT	ORAL	TAB RAPDIS	V
LAMOTRIGINE	LAMOTRIGINE ODT	ORAL	TAB RAPDIS	V
LAMOTRIGINE	LAMICTAL ODT (ORANGE)	ORAL	TB RD DSPK	V
LAMOTRIGINE	LAMOTRIGINE ODT (ORANGE)	ORAL	TB RD DSPK	V
LAMOTRIGINE	LAMICTAL ODT (BLUE)	ORAL	TB RD DSPK	V
LAMOTRIGINE	LAMOTRIGINE ODT (BLUE)	ORAL	TB RD DSPK	V
LAMOTRIGINE	LAMICTAL ODT (GREEN)	ORAL	TB RD DSPK	V
LAMOTRIGINE	LAMOTRIGINE ODT (GREEN)	ORAL	TB RD DSPK	V
LAMOTRIGINE	LAMICTAL XR	ORAL	TAB ER 24	V

LAMOTRIGINE	LAMOTRIGINE ER	ORAL	TAB ER 24	V
LAMOTRIGINE	LAMICTAL XR (BLUE)	ORAL	TB ER DSPK	V
LAMOTRIGINE	LAMICTAL XR (GREEN)	ORAL	TB ER DSPK	V
LAMOTRIGINE	LAMICTAL XR (ORANGE)	ORAL	TB ER DSPK	V
LAMOTRIGINE	LAMICTAL XR	ORAL	TAB ER 24	V
LAMOTRIGINE	LAMOTRIGINE ER	ORAL	TAB ER 24	V
GABAPENTIN	GRALISE	ORAL	TAB ER 24H	N
CARBAMAZEPINE	CARBAMAZEPINE ER	ORAL	CPMP 12HR	N
CARBAMAZEPINE	CARBATROL	ORAL	CPMP 12HR	N
VIGABATRIN	SABRIL	ORAL	POWD PACK	N
VIGABATRIN	SABRIL	ORAL	TABLET	N
FELBAMATE	FELBAMATE	ORAL	ORAL SUSP	N
FELBAMATE	FELBATOL	ORAL	ORAL SUSP	N
FELBAMATE	FELBAMATE	ORAL	TABLET	N
FELBAMATE	FELBATOL	ORAL	TABLET	N
GABAPENTIN	NEURONTIN	ORAL	SOLUTION	N
GABAPENTIN	GABAPENTIN	ORAL	SOLUTION	N
TOPIRAMATE	TOPAMAX	ORAL	CAP SPRINK	N
TOPIRAMATE	TOPIRAMATE	ORAL	CAP SPRINK	N
TOPIRAMATE	TROKENDI XR	ORAL	CAP ER 24H	N
TOPIRAMATE	QUDEXY XR	ORAL	CAP SPR 24	N
TOPIRAMATE	TOPIRAMATE ER	ORAL	CAP SPR 24	N
OXCARBAZEPINE	OXTELLAR XR	ORAL	TAB ER 24H	N
LEVETIRACETAM	KEPPRA XR	ORAL	TAB ER 24H	N
LEVETIRACETAM	LEVETIRACETAM ER	ORAL	TAB ER 24H	N
LEVETIRACETAM	SPRITAM	ORAL	TAB SUSP	N
PREGABALIN	LYRICA	ORAL	CAPSULE	N
PREGABALIN	LYRICA	ORAL	SOLUTION	N
RUFINAMIDE	BANZEL	ORAL	ORAL SUSP	N
LACOSAMIDE	VIMPAT	ORAL	SOLUTION	N
ESLICARBAZEPINE ACETATE	APTIOM	ORAL	TABLET	N
PERAMPANEL	FYCOMPA	ORAL	TABLET	N
PERAMPANEL	FYCOMPA	ORAL	ORAL SUSP	N
BRIVARACETAM	BRIVIACT	ORAL	SOLUTION	N
BRIVARACETAM	BRIVIACT	ORAL	TABLET	N
GABAPENTIN ENACARBIL	HORIZANT	ORAL	TABLET ER	N
CLOBAZAM	ONFI	ORAL	TABLET	N
CLOBAZAM	ONFI	ORAL	ORAL SUSP	N

Appendix 2: Abstracts of Comparative Clinical Trials

Efficacy, safety, and tolerability of lacosamide monotherapy versus controlled-release carbamazepine in patients with newly diagnosed epilepsy: a phase 3, randomised, double-blind, non-inferiority trial.
Baulac, M., Rosenow, F., Toledo, M., et al.
Lancet Neurol. 2017 Jan; 16(1):43-54. doi: 10.1016/S1474-4422(16)30292-7.

BACKGROUND: Further options for monotherapy are needed to treat newly diagnosed epilepsy in adults. We assessed the efficacy, safety, and tolerability of lacosamide as a first-line monotherapy option for these patients.
METHODS: In this phase 3, randomised, double-blind, non-inferiority trial, patients from 185 epilepsy or general neurology centres in Europe, North America, and the Asia Pacific region, aged 16 years or older and with newly diagnosed epilepsy were randomly assigned in a 1:1 ratio, via a computer-generated code, to receive lacosamide monotherapy or controlled-release carbamazepine (carbamazepine-CR) twice daily. Patients, investigators, and trial personnel were masked to treatment allocation. From starting doses of 100 mg/day lacosamide or 200 mg/day carbamazepine-CR, up titration to the first target level of 200 mg/day and 400 mg/day, respectively, took place over 2 weeks. After a 1-week stabilization period, patients entered a 6-month assessment period. If a seizure occurred, the dose was titrated to the next target level (400 or 600 mg/day for lacosamide and 800 or 1200 mg/day for carbamazepine-CR) over 2 weeks with a 1-week stabilization period, and the 6-month assessment period began again. Patients who completed 6 months of treatment and remained seizure-free entered a 6-month maintenance period on the same dose. The primary efficacy outcome was the proportion of patients remaining free from seizures for 6 consecutive months after stabilization at the last assessed dose. The predefined non-inferiority criteria were -12% absolute and -20% relative difference between treatment groups. This trial is registered with ClinicalTrials.gov, number NCT01243177.
FINDINGS: The trial was done between April 27, 2011, and Aug 7, 2015. 888 patients were randomly assigned treatment. 444 patients taking lacosamide and 442 taking carbamazepine-CR were included in the full analysis set (took at least one dose of study treatment), and 408 and 397, respectively, were included in the per-protocol set. In the full analysis set, 327 (74%) patients in the lacosamide group and 308 (70%) in the carbamazepine-CR group completed 6 months of treatment without seizures. The proportion of patients in the full analysis set predicted by the Kaplan-Meier method to be seizure-free at 6 months was 90% taking lacosamide and 91% taking carbamazepine-CR (absolute treatment-difference: -1.3%, 95% CI -5.5 to 2.8 relative treatment difference: -6.0%). Kaplan-Meier estimates results were similar in the per-protocol set (92% and 93%; -1.3%, -5.3 to 2.7; -5.7%). Treatment-emergent adverse events were reported in 328 (74%) patients receiving lacosamide and 332 (75%) receiving carbamazepine-CR. 32 (7%) patients taking lacosamide and 43 (10%) taking carbamazepine-CR had serious treatment-emergent adverse events, and 47 (11%) and 69 (16%), respectively, had treatment-emergent adverse events that led to withdrawal.
INTERPRETATION: Treatment with lacosamide met the predefined non-inferiority criteria when compared with carbamazepine-CR. Therefore, it might be useful as first-line monotherapy for adults with newly diagnosed epilepsy.
FUNDING: UCB Pharma.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 5 2017, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 11, 2017

1	Carbamazepine	11358
2	Diazepam/	18868
3	divalproex.mp. or Valproic Acid/	12820
4	Ethosuximide/	959
5	ethotoin.mp.	48
6	Anticonvulsants/ or gabapentin.mp.	54656
7	lacosamide.mp.	586
8	lamotrigine.mp.	5056
9	levetiracetam.mp.	2734
10	methsuximide.mp.	107
11	oxcarbazepine.mp.	1792
12	Phenobarbital/	18995
13	Phenytoin/	14221
14	Primidone/	1373
15	rufinamide.mp.	211
16	tiagabine.mp.	993
17	topiramate.mp.	4369
18	Valproic Acid/	12589
19	zonisamide.mp.	1239
20	brivaracetam.mp.	136
21	clobazam.mp.	886
22	esclicarbazepine.mp.	2
23	felbamate.mp.	761
24	perampanel.mp.	215
25	Pregabalin/	1784

26	Vigabatrin/	1721
27	1 or 2 or 3 or 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	113635
28	Epilepsy/	74323
29	27 and 28	20504
30	limit 29 to (english language and humans and yr="2016 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	138

Clobazam

Goal(s):

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

Length of Authorization:

- 12 months

Requires PA:

- Clobazam

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient 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.

P&T Review: *3/18 (DM); 7/16; 3/15; 5/12*
Implementation: *8/16, 8/12*

Pregabalin

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

- Pregabalin

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for pregabalin?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 2
2. What diagnosis is being treated?	Record ICD10 code	
3. Does the patient have a diagnosis of epilepsy?	**Yes:** Approve for lifetime	**No:** Go to # 4
4. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Go to # 5	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
5. Has the patient tried and failed gabapentin therapy for 90 days or have contradictions or intolerance to gabapentin?	**Yes**: Approve for 90 days	**No:** Pass to RPh. Deny and recommend trial of gabapentin for 90 days
Renewal Criteria		
1. Does the patient have documented improvement from pregabalin?	**Yes**: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Pregabalin
Funded	
Diabetic Neuropathy	X
Post herpetic Neuropathy	X
Painful Polyneuropathy	X
Spinal Cord Injury Pain	X
Chemotherapy Induced Neuropathy	X
Non-funded	
Fibromyalgia	X

Topiramate

Goal(s):

- Approve topiramate only for funded diagnoses 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:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have diagnosis of epilepsy?	**Yes:** Approve for lifetime (until 12-31-2036)	**No:** Go to #3
3. Does the patient have a diagnosis of migraine?	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime*	**No:** Go to #4
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Has the patient tried or are they contraindicated to at least two of the following drugs? • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic 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. Recommend trial of 2 covered alternatives.
6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #7
7. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate. Use is unfunded: Deny; not funded by the OHP. If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal. 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 Review: *3/18 (DM); 3/17; 7/16; 3/15; 2/12; 9/07; 11/07*
Implementation: *4/18/15; 5/12, 1/12*