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Abbreviated Update: Oral Antiepileptic Drugs

Month/Year of Review: July 2014
End date of literature search: Week 2, April 2014
New drug(s): Eslicarbazepine (Aptiom™)
Manufacturer: Sunovion Inc.

Current Status of PDL Class: See Appendix 1

Research Questions:

- Is there any new relative evidence from high quality systematic reviews or evidence-based guidelines suggesting recommended changes to the current PDL class?
- Is eslicarbazepine more effective than currently available agents?
- Is eslicarbazepine safer than currently available agents?
- Are there unique patients or situations where eslicarbazepine may be more effective or safer than currently available agents?

Conclusions:

- 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[1] and ezogabine has a new Boxed Warning about the risk of permanent retinal abnormalities, vision loss and skin discoloration with its use. [2]
- There is insufficient comparative efficacy and safety evidence for eslicarbazepine versus other AEDs.
- There is high level of evidence[3] 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).

Recommendations:

- Maintain eslicarbazepine (Aptiom) as non-preferred.
- No further research required at this time. Evaluate comparative costs in executive session.

Reason for Review:
In May 2012, the Oregon Pharmacy & Therapeutic Committee (P&T) evaluated the comparative effectiveness evidence of the oral anticonvulsants. Since this review, the Food and Drug Administration (FDA) approved eslicarbazepine (Aptiom™) as adjunctive treatment of partial-onset seizures.[4] Eslicarbazepine's mechanism of action is theorized to reduce seizures by inhibiting voltage-gated sodium channels.[4]

Previous P&T Conclusions and Recommendations (May 2012[5,6,7]):

- There is insufficient evidence to make comparative conclusions about adjunctive treatments for epilepsy.
- Updated NICE guidelines[8] recommend carbamazepine or lamotrigine as first line agents for focal seizures (moderate to very low quality evidence) and sodium valproate as first line treatment for tonic-clonic seizures (low to very low quality evidence).
- Based on a recent AHRQ review,[9] there is insufficient to low strength of evidence suggesting that switching from an innovator to a generic, generic to generic, or generic to innovator version of the same medication increases the short-term risk of hospitalization and hospital stay duration and increases the short -term risk of a composite of having an emergency department and hospitalization visit with or without ambulance service utilization.
- Recommendations were to consider inclusion of all the chemical entities for epilepsy diagnoses but prefer generic alternatives and forms where appropriate and "grandfather" stabilized patients rather than force a change to preferred agents.
- Subsequent New Drug Evaluations have recommended second and third line agents be designated non-preferred (i.e. clobazam, perampanel, ezogabine, felbamate).

Background:
Epilepsy is a common neurological disorder characterized by two or more seizures that are not precipitated by other causes.[10] Antiepileptic drugs (AEDs) to prevent recurrence of seizures are the mainstay of treatment.[8] The overall goals of antiepileptic therapy are to prevent seizures. Reduction in seizure frequency of 50% or more is generally accepted as demonstrating efficacy for FDA approval.[4] When initial drugs have failed and adjunctive treatment is used seizure reduction is likely to be the primary aim.[9] Drug selection is based upon epileptic syndrome, seizure type, the adverse effect profile and patient preference.[8] Despite approximately half of newly diagnosed epileptics being successfully treated with the first AED, treatment failure and drug intolerance can occur. Monotherapy is more likely to promote compliance, reduces potential for drug interactions and is less costly but may not keep a patient seizure free. There are no controlled trials comparing different combinations of AEDs.[12]

Methods:
A Medline literature search through April 2014, week 2, for new systematic reviews that compared AEDs head-to-head for the treatment of epilepsy or randomized controlled trials (RCT's) evaluating eslicarbazepine for the treatment of epilepsy was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high

quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Guidelines:
None identified.

New Systematic Reviews:
No new comparative systematic reviews were identified.

New Safety Information:

Suicide:
In 2009, the FDA issued an alert warning of increased risk of suicide ideation and behavior in patients treated with selected AEDs.[13] A expert consensus statement on this issue was recently published by the ad hoc task force of the Commission on Neuropsychobiology and the International League Against Epilepsy.[14] It notes that the risk of actual suicide is very low.[14] The FDA reports the rate as: AED 0.43% versus placebo 0.24%.[13] The consensus statement stresses that this low absolute risk be balanced with the risks of refusing or stopping AEDs, though the risk was not quantified.

Valproate:
The FDA issued a safety alert for all valproate related products notifying providers that they are contraindicated and should not be taken by women for migraine prophylaxis because it can cause diminished IQ scores in the children born to these mothers.[1] The labeling now indicates these are pregnancy category "X" (from "D").

Ezogabine:
The FDA approved Boxed Warning labeling changes for ezogabine that emphasize the risk of permanent retinal abnormalities, vision loss and skin discoloration with its use. It is to be limited to patients that have not responded adequately to several alternative therapies. Those on ezogabine should be monitored every 6 months for retinal changes by an ophthalmic professional.

Clobazam:
The FDA issued a safety alert for clobazam warning the public that it can cause rare Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). It can happen at any time during treatment but the likelihood is greater in the first 8 weeks of treatment. All 21 reported cases have resulted in hospitalization, one in blindness and one in death. Nineteen cases were associated with other drugs known to be associated with SJS/TEN; however there was a close temporal relationship to initiation of clobazam.

New Drug Evaluation: Eslicarbazepine:

Eslicarbazepine was approved by the FDA November 8, 2013 for adjunctive treatment of partial-onset seizures in adults (see Appendix 2: Specific Drug Information). It was approved by the European Medicines Agency in 2009 based upon 3 phase III studies.[15,16,17] In 2009, the FDA recommended the application not be approved due to "…profound and extensive deficiencies in the conduct and documentation of the studies,…".[4] For this reason, upon resubmission in 2012, the sponsor dropped 303 [NCT00957372].[4] Three studies (301[NCT00957684],[15] 302[NCT00957047],[18] 304[NCT00988429][4]) were considered supportive for the proposed indication. A pooled analysis of 301, 302 and 303 (the study that was dropped in the FDA submission) was recently published but excluded from this evaluation.[19] No active controlled trials were identified.

Cochrane[3] published a systematic review of RCTs of eslicarbazepine versus placebo for adjunctive therapy for drug-resistant partial epilepsy. It included 4 trials[15,18,16, 17] and 1146 patients. The background AED therapy was not described in the systematic review. The overall RR for ≥50% reduction in seizure frequency was 1.86 95% CI 1.46 - 2.36. Patients on eslicarbazepine were more likely to withdraw for adverse events (RR 2.26 95% CI 0.98 - 5.21). The review concluded that eslicarbazepine reduces seizure frequency when used as add-on for drug-resistant partial epilepsy but that the trials were of short-term duration (12-18 weeks) and included adults only. No additional, blinded and published RCTs were identified. Two open-label extension studies have been published but were excluded from this evalutation.[20,21]

Safety was assessed from a database of 4225 patients who were exposed to eslicarbazepine in 53 studies (n=847 healthy volunteers, n=1553 in patients with partial epilepsy, n=1832 in non-epilepsy patients).[4] Rare serious adverse events are similar to other drugs in the class (i.e. suicidal ideation, SJS/TEN, drug reaction with eosinophilia and systemic symptoms, anaphylaxis, hyponatremia, neurological disturbances and hepatic injury. Patients should be tapered off eslicarbazepine to minimize the risk of seizures. There were dose dependent decreases in T3 and T4 serum test but the changes were not associated with other abnormal thyroid function tests.

The NICE guidelines[8] recommend eslicarbazepine as third-line for partial epilepsy.

There is potential for off-label uses as the FDA noted 36 studies were submitted with the first application and 17 new studies with the approved submission.[4] Clinicaltrials.gov lists 28 studies involving eslicarbazepine (a.k.a. BIA-2093); 3 Phase II for Bipolar I, 3 for diabetic neuropathic pain (1 each Phase I, II, III), 1 Phase II for migraine prophylaxis, 1 Phase II for Fibromyalgia, 2 (1 each Phase I, II), and 2 for post-herpetic neuralgia (1 each Phase II, III) and 18 for Epilepsy or Partial Epilepsy (8 Phase I, 2 Phase II, 9 Phase III, 1 Phase IV and 1 unknown).

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Appendix 1 – Current PDL Status

Preferred	
GENERIC NAME	**FORM**
CARBAMAZEPINE	ORAL SUSP
CARBAMAZEPINE	TAB CHEW
CARBAMAZEPINE	TAB ER 12H
CARBAMAZEPINE	TABLET
DIVALPROEX	CAP SPRINK
DIVALPROEX	TAB ER 24H
DIVALPROEX	TAB DR
ETHOSUXIMIDE	CAPSULE
ETHOSUXIMIDE	SOLUTION
ETHOTOIN	TABLET
GABAPENTIN	CAPSULE
LACOSAMIDE	TABLET
LAMOTRIGINE	TABLET
LEVETIRACETAM	SOLUTION
LEVETIRACETAM	TABLET
METHOSUXIMIDE	CAPSULE
OXCARBAZEPINE	ORAL SUSP
OXCARBAZEPINE	TABLET
PHENOBARBITAL	ELIXER
PHENOBARBITAL	TABLET
PHENYTOIN	ORAL SUSP
PHENYTOIN	TAB CHEW
PHENYTOIN EXTENDED	CAPSULE
RUFINAMIDE	TABLET
TIAGABINE	TABLET
TOPIRAMATE	TABLET
VALPROIC ACID	CAPSULE
VALPROIC ACID	SOLUTION
ZONISAMIDE	CAPSULE

Non-Preferred	
GENERIC NAME	**FORM**
CARBAMAZEPINE	CPMP 12 HR
CLOBAZAM	ORAL SUSP
EZOGABINE	TABLET
FELBAMATE	ORAL SUSP
FELBAMATE	TABLET
GABAPENTIN	SOLUTION
GABAPENTIN	TABLET
LACOSAMIDE	SOLUTION
LEVETIRACETAM	TAB ER 24H
OXCARBAZEPINE	TAB ER 24H
PERAMPANEL	TABLET
PREGABLIN	SOLUTION
PREGABLIN	CAPSULE
RUFINAMIDE	ORAL SUSP
TOPIRAMATE	CAP ER 24H
TOPIRAMATE	CAP SPRINK
VIGABATRIN	POWD PACK
VIGABATRIN	TABLET
LAMOTRIGINE	TAB ER 24H
LAMOTRIGINE	TAB RAPIDIS
LAMOTRIGINE	TB CHW DSP
LAMOTRIGINE	TB ER DSPK
LAMOTRIGINE	TB RD DSPK
VALPROIC ACID	CAPSULE DR

Appendix 2: Specific Drug Information[4]

CLINICAL PHARMACOLOGY: Eslicarbazepine is a novel, once daily AED thought to reduce seizures by inhibition of the voltage-gated sodium channels. It is chemically related to carbamazepine and oxcarbazepine but does not inhibit most P450 enzymes, thus has reduced risk of drug-drug interactions. Clearance is dependent on renal function.

PHARMACOKINETICS:

Parameter	Result
Oral Bioavailability	91% after first-past metabolism to active form
Protein Binding	<40%
Elimination	90% & glucoronide conjugates excreted in urine; other 10% of minor metabolites excreted in urine
Half-Life	13-20 hours; steady-state in 4-5 days
Metabolism	hydrolytic first-pass to active metabolite (eslicarbazepine from acetate salt)

DOSE & AVAILABILITY:

AVAILABLE STRENGTH	FORM	FREQUENCY	RENAL ADJ	HEPATIC ADJ	PED DOSE	GER DOSE	OTHER
200MG 400MG 600MG 800MG	TABLET (DO NOT CRUSH)	Initiate at 400mg QD x 7 days then increase to 800mg QD. Maximum: 1200mg QD (after minimum of 1 week at 800mg QD)	CrCl <50ml/min: Initiate at 200mg QD x 14 days then increase to 400mg (recommended maintenance)	NA	NA	NA	Taper required for discontinuance. Pregnancy Category: C

DRUG SAFETY:

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

Warnings and Precautions: Suicidal Behavior and Ideation, Serious Dermatologic Reactions, Drug Reaction with Eosinophilia and Systemic Symptoms, Anaphylactic Reactions and Angioedema, Hyponatremia, Neurological Adverse Reactions (e.g. dizziness, disturbance of gait, somnolence, etc.), Drug Induced Liver Injury.