Therapeutic Class Review[SM]

Neurological: Seizure medications
lacosamide (Vimpat®) & rufinamide (Banzel®)

April 2009

Executive Summary

New Products for Review:
lacosamide (Vimpat)[Schwarz Biosciences]
rufinamide (Banzel)[Eisai, Inc]

Dossier Provided by Manufacturer:
Dossier Evaluation:
Vimpat: 3
Banzel: not available as of 3/11/2009

1 - Dossier missing significant clinical trial(s).
2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
3 - Mfg. provided all relevant trials and information.

Background

- No antiepileptic drugs (AED) treat all types of epilepsy, and combination therapy is often needed to minimize seizures. [1] Treatment is highly individualized to type of disorder, comorbidities, concomitant medications, and patient response.
- The two recently approved AEDs, lacosamide (Vimpat) and rufinamide (Banzel), join a large cohort of seizure medications, many of which are now available as low cost generics. Several more AEDs are in late stage development.
- The Regence preferred medication list/formulary contains generic and preferred/formulary brand alternatives for various types of seizures, including partial onset and Lennox-Gastaut Syndrome (LGS).
- It is possible that lacosamide (Vimpat) or rufinamide (Banzel), like other AEDs, will be used to treat other seizure types and a variety of other off-label uses (including pain relief, mental health disorders, etc.). Lacosamide (Vimpat) is being studied as monotherapy for partial onset seizures, diabetic neuropathy and fibromyalgia. A trial in partial onset seizures is underway with rufinamide (Banzel). [17]

Evidence summary

AEDs [2,11,12,13,14]

- Research efforts focus on the discovery and development of more effective and less toxic AEDs that have a simplified, once daily dosing regimen, rather than comparative research. Consequently, there is insufficient evidence to determine if one drug offers better overall efficacy or safety.
- Clinical practice guidelines and systematic reviews conclude AEDs are more effective than placebo at reducing seizure frequency, but carry risk of significant adverse effects. No one

medication or combination of AEDs is recognized as superior to other regimens, so treatment is individualized to patient factors.
- The majority of members using a preferred brand AED are on a product with no black box warnings.

Lacosamide (Vimpat):

- There were three randomized, controlled clinical trials evaluated for this review.
- All three were critiqued as not useful for making healthcare decisions because of significant threats to reliability, including large numbers of patient drop-outs.

Rufinamide (Banzel):

- One randomized, controlled clinical trial was evaluated for this review.
- This trial was critiqued as not useful for making healthcare decisions because of significant threats to reliability and imbalances between groups in drop-out rates.

Expert Opinion

Expert opinion was sought from seven neurologists in February, 2009. No comments were received.

Practical Considerations

	Lacosamide (Vimpat)	**Rufinamide (Banzel)**
Incidence and severity	Partial onset seizures are somewhat common. A significant portion of patients are uncontrolled on currently available therapies.	LGS is a rare, severe form of seizure.
Potential for off-label use	AEDs are commonly used for a variety of off-label conditions.	
Other treatment options	There are several generic and brand formulary/preferred alternatives for treatment of partial onset seizures.	There are generic and brand preferred/formulary alternatives for treatment of LGS.
Potential magnitude of clinical benefit	May result in a modest reduction in seizures when used as add-on therapy, although the evidence for efficacy is uncertain.	
Safety	No proven advantage.	
Drug-drug interactions	Low potential for drug-drug interactions.	Banzel affects the pharmacokinetics of several classes of drugs, including other AEDs, but the clinical significance of these interactions is uncertain.
Clinical practice perspective	Treatment is highly individualized and there is a need for options that fit specific patient needs. Clinicians have a resistance to making changes to an effective AED regimen.	

Product Value

- Lacosamide (Vimpat) appears to add no proven additional value over current medication options for the treatment of partial onset seizures and may have a safety advantage in some situations.
- Rufinamide (Banzel) appears to add no proven additional value over current medication options for the treatment of Lennox-Gastaut Syndrome.

Decision

Maintain lacosamide (Vimpat) and rufinamide (Banzel) as non-preferred/non-formulary because:

- There is no useful evidence that these products are safer or more effective than other available AEDs.

- There are multiple generic and preferred/formulary brand AEDs available to meet the needs of most members, including those with partial onset seizures and LGS.

I. Products

A. Approved AEDs

Drug Products	FDA approval [a]	Patent Expir-ation(s)[c]	FDA approved indications	Usual Dose/Route	Potential Off-label Uses[d]
Vimpat (lacosamide)	10/2008	10/2013	Epilepsy: adjunctive use for **partial** onset seizures**.**	Oral tablet and IV. Maximum 400 mg per day.	AEDs have been used off-label in a variety of conditions such as bipolar disorder, cocaine addiction, dementia, depression, diabetic peripheral neuropathy, fibromyalgia, headache, hiccoughs, Huntington's disease, mania, migraine, obsessive compulsive disorder, panic disorder, restless leg syndrome, tinnitus.
Banzel (rufinamide)	11/2008	11/2013	Epilepsy: adjunctive use for **LGS**	Oral tablet. Maximum 3,200 mg per day.	
Tegretol (carbamazepine)		expired	Epilepsy: grand mal, **partial**, or mixed seizures. Trigeminal neuralgia.	Oral tablet and suspension. 800 mg – 1,200 mg per day.	
Tegretol XR (carbamazepine extended release)		expired		Oral tablet. Maximum 1,600 mg per day.	
Carbatrol (carbamazepine extended release)	9/1997	7/2011		Oral capsule. Maximum of 1,600 mg per day.	
Neurontin (gabapentin)		expired	Epilepsy: adjunctive use for **partial** seizures Post-herpetic neuralgia	Oral tablet, capsule and solution. Maximum 1,800 mg per day.	
Lamictal (lamotrigine)		expired	Epilepsy: adjunctive use for partial seizures, Lennox-Gastaut syndrome (**LGS**), generalized tonic-clonic seizures; monotherapy for **partial** seizures. Bipolar disorder	Oral tablet. Maximum 700 mg per day.	
Keppra (levetiracetam)		expired	Epilepsy: adjunctive use for **partial** onset, myoclonic, and generalized tonic-clonic seizures.	Oral tablet and IV. Maximum 3,000 mg per day.	
Keppra XR (levetiracetam extended release)	9/2008	9/2011	Epilepsy: adjunctive use for **partial** onset seizures.	Oral tablet. Maximum 3,000 mg per day.	
Zonegran (zonisamide)		expired	Epilepsy: adjunctive use for **partial** seizures	Oral capsule. Maximum 600 mg per day.	
Gabitril (tiagabine)	9/1997	9/2011	Epilepsy: adjunctive use for **partial** seizures	Oral tablet. Maximum 56 mg per day.	
phenobarbital		expired	Epilepsy: tonic-clonic and simple **partial** seizures.	Oral tablet and elixir. IV/IM. Usual oral dose 120 mg - 180 mg per day. Various IV/IM regimens.	
Dilantin (phenytoin) tablets		expired	Epilepsy: tonic-clonic (grand mal) and complex **partial** seizures	Oral capsule, tablet, and suspension; adults: 300 mg -400 mg per day., children: 5 - 8 mg/kg per day. Various IV/IM regimens.	
Dilantin (phenytoin) extended release capsules		expired			

Drug Products	FDA approval [a]	Patent Expir-ation(s)[c]	FDA approved indications	Usual Dose/Route	Potential Off-label Uses[d]
Mysoline (primidone)		expired	Epilepsy: tonic-clonic (grand mal) and **partial** seizures	Oral tablet. Maximum 2,000 mg per day.	
Topamax (topiramate)	12/1996	expired	Epilepsy: adjunctive and monotherapy for **partial** onset and generalized tonic-clonic seizures; adjunctive therapy for **LGS**. Migraine	Oral tablet and capsule. Maximum 400 mg per day.	
Felbatol (felbamate)	7/1993	9/2009	Epilepsy: monotherapy or adjunctive therapy for **partial** onset seizures, with and without generalization in adults and generalized seizures associated with **LGS** in children.	Oral tablet and suspension. Maximum 3,600 mg per day.	
Depakene (valproic acid)	Before 1982	expired	Epilepsy: simple and complex absence, **partial** seizures. Bipolar disorder, migraine prophylaxis	Oral capsule and syrup. Maximum of 60 mg/kg per day.	
Depakote (divalproex)	3/1983	expired	Epilepsy: adjunctive and monotherapy use for complex **partial** seizures, simple & complex absence seizures; adjunctive use for multiple seizure types. Migraine Mania associated with bipolar disease	Oral tablet. Maximum 60 mg/kg per day.	
Depakote ER (divalproex extended release)	8/2000	expired		Oral tablet. Maximum 60 mg/kg per day.	

[a] Date applies to approval date for the original brand name medication where there are now generics available.
[c] Based on patents listed in Orange Book as of 12/23/2008.
[d] As listed in © 1974 - 2008 Thomson MICROMEDEX database or as referenced.

B. Pipeline products

Drug Products	Status*	Potential indication(s)	Other	Comments
Valrocemide, YKP 509, TV1901 [Shire]	Anticipated launch- 2009	Epilepsy and bipolar disorder.	Combination of valproic acid and glycinamide, an amino acid with antiepileptic properties.	Valrocemide is essentially a prodrug, converted in the brain to its biologically active form.
Vigabatrin (Sabril)[Ovation]	Anticipated launch: 2009	Complex **partial** seizures, cocaine and meth addiction.	GABA transaminase inhibitor. Oral tablet taken 1-2 times daily.	FDA granted priority review designation; would be first approved product for stimulant addiction. Marketed in Europe since late 1980s. Also available in Canada. Major safety issue is retinal damage with long term use, which may be irreversible.
Carisbamate (Comfyde)[J&J]	NDA filed 10/2008 Anticipated launch: 2011	**Partial** onset seizures in patients $\geq$ 16 yrs of age.	Oral tablet taken every 12 hours.	Three placebo-controlled CTs were in filing. Ortho-McNeil to market product in US.
Retigabine [Valeant]	Phase III trials Completion date: 3/2008 NDA filing planned for mid-2008	Adjunctive therapy for treatment of refractory **partial** onset seizures.	Oral tablet, taken 3 times daily. Potassium channel opener.	NCT00232596 "RESTORE 1" NCT00235755 "RESTORE 2" Claims to be first-in-class neuronal potassium channel opener

B. Pipeline products (continued)

Drug Products	Status*	Potential indication(s)	Other	Comments
Clobazam [Ovation]	Phase III trial Completion date: 5/2009	**LGS**	Oral tablet taken twice daily. A member of the benzodiazepine class, acts to regulate GABA and glutamate transport.	NCT00518713 Granted orphan drug status for treatment of LGS in Jan 2008. Currently marketed for treatment of epilepsy and anxiety in over 100 countries outside the US.
Oxcarbazepine extended release (Epliga)[Superna]	Phase III trials Completion date: 12/2009	Adjunctive therapy for treatment of refractory **partial** onset seizures.	Once daily oral formulation.	NCT00772603 Claims potential for improved compliance, fewer AEs compared to Trileptal (immediate release oxcarbazepine).
Carvedilol-controlled release (Coreg-CR)[GSK]	Marketed for cardiovascular disease. Phase III epilepsy trial Completion date: 12/2009	Adjunctive therapy for refractory primary generalized or symptomatic generalized epilepsy.	Oral capsule taken once daily.	NCT00524134
Perampanel, E2007[Eisai]	Phase III trials Completion date: 9/2010 NDA filing planned for 2012	Adjunctive therapy for treatment of refractory **partial** onset seizures.	Oral tablet taken once daily. Glutamate receptor antagonist.	NCT00699972 Claims to be first-in-class, orally administered, selective AMPA-type glutamate receptor antagonist.
Brivaracetam [UCB]	Phase III trials Completion date: 04/2011	Treatment of refractory **partial** onset seizures (as adjunctive or monotherapy).	Oral tablet taken twice daily. Analog of levetiracetram (Keppra) [UCB]	NCT00464269 NCT00699283 Granted orphan drug status for myoclonus in Dec 2005.

* status as of 12/2008

References

1. Centerwatch: report on products in the pipeline for epilepsy. [page on the internet] Available at http://www.centerwatch.com/professional/cwpipeline/eyeon_epilepsy.html. Accessed 12/24/2008.
2. Wilner, AN. Neuropharmacology of Antiepileptic Drugs. Available at http://www.medscape.com/viewarticle/423305. Accessed 12/24/2008.
3. Drugs@FDA [page on the internet]. FDA review documents for lacosamide (Vimpat). Available at: http://www.fda.gov/cder/foi/nda/2008/022253s000_022254s000TOC.htm. Accessed 2/1/2009.
4. Ben-Menachem E, Biton V, Jatuzis D, Abou-Khalil B, Doty P, Rudd GD. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. *Epilepsia* 2007 Jul; 48(7):1308-17.
5. Glauser T, Kluger G, Sachdeo R, Krauss G, Perdomo C, Arroyo S. Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. *Neurology* 2008;70:1950-1958.
6. Vimpat Product Information. UCB Inc. Smyrna, GA. October 2008.
7. Product dossier: Vimpat (lacosamide), UCB, Inc.; Smyrna, GA. Data reviewed February 2009.
8. Banzel Product Information. Eisai Co Ltd, Woodcliffe Lake, NJ. November 2008.
9. FDA News release. FDA Requires Warning about Risk of Suicidal Thoughts and Behavior for antiepileptic Medications. [page on the internet] Available at http://www.fda.gov/bbs/topics/NEWS/2008/NEW01927.html. Accessed 12/17/2008.
10. Medicines and Healthcare Products Regulatory Agency [page on the internet]. Product-specific information and advice: Antiepileptics. Available at http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Antiepileptics/index.htm. Accessed February 2009.
11. Hancock E, Cross H. Treatment of Lennox-Gastaut syndrome. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art.No.:CD003277. DOI: 10.1002/14651858.
12. Marson A, Maguire M, Ramaratnam S. Clinical Evidence Review: Epilepsy. Available at http://clinical evidence.bmj.com/ceweb/conditions/nud/1201/1201_I11.jsp. Accessed on 1/27/2009.
13. French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, et al. Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy: Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2004;62:1252-60.
14. French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, et al. Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy: Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2004;62:1261-73.
15. Halasz P, Kalviainen R, Mazurkiewicz-Beldzinska M, Rosenow F, Doty P, Hebert D, Sullivan S. Adjunctive Lacosamide for partial-onset seizures: Efficacy and safety results from a randomized controlled trial. *Epilepsia* 2009 Jan 17. [epub ahead of print].
16. Chapple C. Fesoterodine a new effective and well-tolerated antimuscarinic for the treatment of urgency-frequency syndrome:results of a phse 2 controlled study. *Neurol Urodyn* 2004;23:598-9.
17. ClinicalTrials.Gov; lacosamide (Vimpat) trials. Available at : http://clinicaltrials.gov/ct2/results?term=lacosamide. Accessed March 11, 2009.