An overview of third-generation antiseizure drugs

Clobazam, lacosamide, rufinamide, and vigabatrin

Marianna V. Spanaki, MD, PhD, MBA

Gregory L. Barkley, MD

Summary

Four antiseizure drugs have been approved in the United States since 2008. Clobazam, a 1,5-benzodiazepine, was approved in October 2011 as an adjunctive therapy for Lennox-Gastaut syndrome (LGS) in patients 2 years and older. Lacosamide, an amino acid that selectively enhances the slow inactivation of voltage-gated sodium channels, was approved in October 2008 as an add-on therapy for partial onset seizures in patients 17 years and older. Rufinamide, a triazole derivative, was approved in November 2008 as an adjunctive therapy for LGS in patients 4 years and older. Vigabatrin, an irreversible inhibitor of GABA transaminase, was approved in August 2009 for the treatment of infantile spasms in children ages 1 month to 2 years and intractable complex partial seizures in adults.

Clobazam, lacosamide, rufinamide, and vigabatrin are new antiseizure drugs (ASDs) which have been approved since 2008 for use in the United States. Each of these ASDs will be reviewed in this article. To make it easier for readers to compare some of the key features of each medication, a summary overview table of these drugs can be found on page 239.

Clobazam

Indications Clobazam (CLB) is approved as an adjunctive treatment for Lennox-Gastaut syndrome (LGS) in adults and children 2 years of age and older.

Henry Ford Comprehensive Epilepsy Program, Detroit, MI.

Correspondence to: mspanak1@hfhs.org

Rufinamide may exert its anticonvulsant action by prolongation of the inactive state of sodium channels and inhibition of the firing of sodium-dependent action potentials.

Mechanism of action CLB, a 1,5-benzodiazepine, enhances γ -aminobutyric acid (GABA)-ergic inhibition by binding to the GABA_A receptors.¹

Pharmacology CLB is completely absorbed following oral administration with peak plasma levels in 1–4 hours and elimination half-life 18 hours. It is 90% protein bound and it is metabolized by N-demethylation by CYP3A4 and to a lesser extent by CYP2C19 and CYP2B6. There are no drug interactions with other ASDs.¹ In one study, phenytoin (PHT) intoxication was reported in 3 patients when CLB was added to PHT.² This may be due to interference with the CYP2C19 component of PHT metabolism.

Clinical trials A total of 238 patients (2–60 years) with LGS were included in a double-blind, placebo-controlled, clinical phase III study.³ The mean percentage reduction in average weekly rate of drop seizures was 41.2%, 49.5%, and 68.3% at doses 0.25, 0.5, and 1.0 mg/kg/day, respectively.³ Responder rates were 43.4%, 58.6%, and 77.6% for the 0.25, 0.5, and 1.0 mg/kg/day groups, respectively.³

Adverse effects Adverse effects reported for more than 10% of patients at any dose include somnolence and sedation in 26%, pyrexia in 13%, urinary tract infection in 12%, and lethargy in 10%.⁴ Aggression, irritability, and drooling occurred in less than 10%.⁴ Since CLB is highly protein bound, conditions that alter protein concentrations such as liver disease and older age lead to higher free drug levels and toxicity.

Dosage and administration CLB (Onfi™, Lundbeck) is available in 5, 10, and 20 mg tablets. Recommended starting dose in adults is 5 mg twice a day followed by a 10 mg increase every 1–2 weeks up to 20 mg twice a day.⁴ Doses up to 60 mg a day in 2 divided doses are tolerated. The average cost for 30 tablets of 5, 10, and 20 mg is \$100, \$200, and \$400, respectively.

Lacosamide

Indication Lacosamide (LCM) was approved as an add-on therapy for partial onset seizures in patients 17 years and older.

Mechanism of action LCM, a fractionalized amino acid, selectively enhances slow inactivation of voltage-gated sodium channels.^{5,6}

Pharmacology LCM is absorbed in 4 hours and food does not affect bioavailability. It is eliminated by renal excretion (40%) and biotransformation. It is 15% protein bound with a half-life of 13 hours. It reaches steady state in 3 days. Although it has no effect on the concentration of concomitant ASDs, its blood level is decreased by 15%–20% by enzyme-inducing ASDs.^{5,6}

Clinical trials Three randomized, double-blind, placebo-controlled, multicenter trials were conducted in patients with poorly controlled partial-onset seizures with or without secondary generalization. Different doses of LCM were compared to placebo: SP667 (n = 418; 200, 400, and 600 mg/day), SP754 (n = 405; 400 and 600 mg/day), and SP755 (n = 485; 200 and 400 mg/day). All studies showed a statistically significant effect in outcome measures (50% responder rate and median percentage seizure reduction) at 400 mg and 2 studies (SP667 and SP775) at 600 mg/day.^{5,6}

Vigabatrin (VGB) is approved as monotherapy in the treatment of infantile spasms in children ages 1 month to 2 years and add-on in adults with refractory complex partial seizures.

There is limited experience in the treatment of status epilepticus using LCM since currently available studies have provided only Class IIb, Level C evidence.⁷

Adverse effects Common side effects (in more than 5% of subjects) were dizziness, headache, fatigue, nausea, diplopia, ataxia, tremor, back pain, and upper respiratory tract infection. Psychosis was reported in only 0.3%.^{5,6}

Precautions LCM should be avoided in severe hepatic impairment. The maximum daily dose should not exceed 300 mg in mild to moderate hepatic impairment and if creatinine clearance is less than 30 mL/min. Following dialysis, 50% of the dose of LCM should be supplemented.

LCM can cause prolongation of PR interval and should be used with caution in patients with severe cardiac disease or those taking medication such as β -blockers, calcium channel blockers, and amiodarone. Syncope, atrial fibrillation, and flutter have been reported. An ECG should be performed in patients with cardiac disease before treatment and when steady state is achieved.⁵

Dosage and administration LCM (VIMPAT UCB) is available in 50, 100, 150, and 200 mg tablets and oral solution 10 mg/mL. Starting dose is 50 mg twice a day followed by weekly increases of 100 mg in two divided doses up to 200 mg twice a day. Doses of 600 mg/day may be slightly more efficacious than 400 mg/day but less tolerated.^{5,6}

The IV solution is available in a 200 mg/20 mL single dose vial and is compatible with dextrose, sodium chloride 0.9%, and lactated Ringers. It is recommended to be infused over 30–60 minutes.⁵

The monthly cost is \$260–\$475 for the tablets and \$23 per one 200-mg vial.⁵

Rufinamide

Indication Rufinamide (RFM) is approved as an adjunctive therapy for LGS in patients 4 years and older.

Mechanism of action RFM, a triazole, is chemically unrelated to current ASDs. Rufinamide may exert its anticonvulsant action by prolongation of the inactive state of sodium channels and inhibition of the firing of sodium-dependent action potentials.⁸

Pharmacology RFM is a lipophilic compound absorbed in the small bowel. Bioavailability is increased with food.⁸ RFM is only 34% protein bound with a mean half-life of 9 hours in adults and peak plasma concentrations in 6.6 hours. Its metabolism is not via cytochrome P450 and approximately 85% of the drug is renally excreted. It lacks significant drug-to-drug interactions when it is coadministered with carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. However, addition of valproic acid increases the levels of RFM by 40% in children and 11% in adults. Therefore, adjustment in RFM dose may be required with the initiation or withdrawal of valproic acid.⁸

Clinical trials In a multicenter, randomized, placebo-controlled parallel-group study in 138 patients with LGS (mean age = 14) followed by an open label extension period, the median seizure reduction of all seizures from baseline was –32.7% for RFM vs –11.7% for placebo. A total of 4.1% showed 100% reduction in tonic-atonic seizures.⁸ Another double-blind,

Table Overview of third-generation ASDs (mechanism of action, indications, forms, recommended dosing, adverse effects, interactions)

ASD	Mechanism of action	Indications	Forms	Dosing	Adverse effects	Interactions
Clobazam (Onfi, Lundbeck)	Enhances GABAergic inhibition	LGS > 2 y/o	Tablets 5 mg, 10 mg, 20 mg	Adults: 5 mg BID increase by 10 mg every week up to max 20 mg BID	Somnolence, sedation, pyrexia, urinary tract infection	Increases levels of PHT
Lacosamide (VIMPAT, UCB)	Slow inactivation of VGSCs	Add-on CPS > 17 y/o	Tablets 50 mg, 100 mg, 200 mg, IV single dose vial 200 mg/20 mL	200 mg BID	Dizziness, headache, fatigue, nausea, diplopia, ataxia, tremor	Enzyme-inducing ASDs decrease levels by 15%–20%
					Avoid in severe hepatic, renal, cardiac disease	
Rufinamide (Banzel, Eisai)	Prolongation of inactive state of Na ⁺ channels	Add-on LGS > 4 y/o	Tablets 200 mg, 400 mg	Children: 10 mg/kg/day increase by 10 mg/kg/day QOD (max 45 mg/kg/day)	Fatigue, dizziness, nausea, vomiting, somnolence, diplopia	Addition of VPA increases level by 40% in adults and 11% in children
			Suspension 40 mg/mL	Adults: 400–800 mg/day increase by 400–800 mg QOD (max 3,200 mg)	QT interval decreases	
Vigabatrin (Sabril, Lundbeck)	Inhibits GABA-T	Infantile spasms (1 month–1 y/o) and adults with refractory CPS	Tablets 500 mg, powder packets 500 mg	Children: 15 mg/kg/day increase by 25–50 mg/kg/day (max 150 mg/kg/day)	Headaches, somnolence, fatigue, dizziness, convulsion	Decreases levels of PHT
				Adults: 500 mg BID (max 3 g/day)	Black box warning: permanent, bilateral concentric field defect	

Abbreviations: ASD = antiseizure drug; CPS = complex partial seizure; GABA = γ -aminobutyric acid; GABA-T = GABA transaminase; LGS = Lennox-Gastaut syndrome; PHT = phenytoin; VGSC = voltage-gated sodium channel; VPA = valproic acid.

placebo-controlled, randomized, parallel-group, multicenter trial in adults >16 years of age with intractable partial seizures showed that adjunctive treatment with RFM resulted in 20.4% medial reduction in partial seizures.⁹

Adverse effects The most common side effects included fatigue (17%), dizziness (13%), nausea (9%), vomiting (7%), somnolence (7%), and diplopia (6%). Cognitive or psychiatric side effects occurred at lower rate than placebo. Side effects rate slightly increases in adults and with high plasma concentrations.^{8,9} Discontinuation of treatment due to side effects was reported in 12.5% in children⁸ and 13.5% in adults.⁹

Precautions It is contraindicated in patients with short QT interval. It is advised to obtain an ECG prior to initiating treatment.⁸

Dosage and administration RFM (Banzel, Eisai) is available in 200 and 400 mg tablets and oral suspension 40 mg/mL.

For children, the starting dose is 10 mg/kg/day in two divided doses increased by 10 mg/kg/day every other day up to 45 mg/kg/day; for adults 400–800 mg a day with increases every

other day by 400–800 mg a day up to 3,200 mg in 2 equally divided doses.^{8,9} When RFM is added to valproic acid, the starting dose should be lower than 400 mg.^{8,9}

The average cost for 90 tablets of 200 mg and 400 mg is \$340–\$380 and \$740–\$760, respectively.

Vigabatrin

Indications Vigabatrin (VGB) is approved as monotherapy in the treatment of infantile spasms in children ages 1 month to 2 years and add-on in adults with refractory complex partial seizures.

Mechanism of action VGB increases the levels of GABA in the brain by irreversibly inhibiting the enzyme GABA transaminase.¹⁰

Pharmacology VGB is rapidly absorbed. It is not protein bound and has an elimination half-life of 5–7 hours. However, since VGB is an irreversible inhibitor of GABA transaminase, it increases the levels of GABA in the brain. The levels of GABA increase in the brain and return to a baseline level only after 5 days. In other words, the levels of VGB in the blood are irrelevant to the effect of VGB in the brain. VGB is eliminated primarily via the kidneys (65% of the administered dose is found unchanged in the urine within 24 hours). Although VGB lacks drug-drug interactions, it is reported to decrease the plasma concentration of phenytoin by 16%–20%.¹⁰

Clinical trials Study 1 (n = 174), a randomized, double blind, placebo-controlled, dose-response study on 174, showed that 51% and 53% of patients randomized to VGB 3 g/day and 6 g/day, respectively, experienced a 50% or greater reduction in CPS compared to 9% on placebo.

Study 2 (n = 183), a randomized, double-blind, placebo-controlled, parallel study, showed that VGB 3 g/day was statistically significantly superior to placebo in reducing seizure frequency.¹⁰

Adverse effects There is a black box warning that describes the risk of permanent bilateral concentric visual field defects in 30%–40% of patients following 6–24 months of treatment.¹⁰

The most common adverse effects are headaches (18%), somnolence (17%), fatigue (16%), dizziness (15%), convulsion (11%), nasopharyngitis (10%), weight gain (10%), and upper respiratory tract infection (10%).

Precautions Goldman kinetic perimetry is recommended at baseline and every 3 months during therapy and in 3–6 months after the discontinuation of VGB.¹⁰

Dosage and administration VGB (Sabril, Lundbeck) is available through a manufacturer-sponsored, restricted distribution program (SHARE at 1-888-45-SHARE) in 500 mg tablets and 500 mg powder packets (each packet is mixed with 10 mL of water to make a solution with a concentration of 50 mg/mL).

The initial daily dose for children is 15 mg/kg/day in 2 divided doses and can be titrated every 3 days by increments of 25–50 mg/kg/day up to 150 mg/kg/day. For adults, starting dose is 500 mg twice a day and can be increased by 500 mg every week up to 3 g/day. Fifty VGB packets cost approximately \$1,500.

REFERENCES

1. Hanks GW. Clobazam: pharmacological and therapeutic profile. *Br J Clin Pharmacol* 1979;7:151S–155S.
2. Zifkin B, Sherwin A, Andermann F. Phenytoin toxicity due to interaction with clobazam. *Neurology* 1991;41:313–314.
3. Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA; OV-1012 Study Investigators. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. *Neurology* 2011;77:1473–1481.
4. Onfi TM. Full prescribing information. Lundbeck Inc [online]. Available at: <http://www.lundbeckinc.com/us/products/cns-products/onfi>. Accessed July 8, 2012.
5. Harris JA, Murphy JA. Lacosamide: an adjunctive agent for partial-onset seizures and potential therapy for neuropathic pain. *Ann Pharmacother* 2009;43:1809–1817.
6. Halford JJ, Lapointe M. Clinical perspectives on lacosamide. *Epilepsy Curr* 2009; 9:1–9.

7. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 2012;17:3–23.
8. Gresham J, Eiland LS, Chung AM. Treating Lennox-Gastaut syndrome in epileptic pediatric patients with third generation rufinamide. *Neuropsychiatr Dis Treat* 2010;6:639–645.
9. Brodie MJ, Rosenfeld WE, Vazquez B, et al. Rufinamide for the adjunctive treatment of partial seizures in adults and adolescents: a randomized placebo-controlled trial. *Epilepsia* 2009;50:1899–1909.
10. Sabril Full prescribing information. Lundbeck Inc [online]. Available at: http://www.lundbeck.com/upload/us/files/pdf/Products/Sabril_MG_US_EN.pdf. Accessed July 8, 2012.

DISCLOSURES

M. Spanaki reports no disclosures relevant to the manuscript. G. Barkley is currently a dunes investigator on a NeuroPace device trial and previously an investigator in clinical trials leading to the approval of lacosamide and rufinamide. Go to Neurology.org/cp for full disclosures.

Related articles from other AAN physician and patient resources

Neurology® ● www.neurology.org

Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome

October 11, 2011; 77:1473–1481.

Rufinamide for generalized seizures associated with Lennox–Gastaut syndrome

May 20, 2008; 70:1950–1958.

Neurology Today® ● www.neurotodayonline.com

FDA Approves Clobazam for Reducing Lennox-Gastaut Seizures

November 3, 2011; 11:42.

‘Next Generation’ Antiseizure Drugs Bubbling Through the Developmental Pipeline

January 15, 2009; 9:18.