

Therapeutic Class Overview Anticonvulsants

Therapeutic Class

Overview/Summary: The anticonvulsants class encompasses over 20 different chemical entities including barbiturates, benzodiazepines, hydantoins, succinimides, and miscellaneous anticonvulsants. These agents are Food and Drug Administration (FDA)-approved for the prevention and/or treatment of various seizure disorders either as monotherapy or adjunctive therapy. The goals of epilepsy management are to control seizures, avoid treatment side effects and maintain or restore patients' quality of life. Anticonvulsants work by various mechanisms of action to achieve these treatment goals, often by stabilizing neuronal membranes in the brain to reduce seizure activity and to elevate the seizure threshold. Some anticonvulsants are also FDA-approved for the prevention of migraines and the management of bipolar disorder, fibromyalgia, neuropathic pain, along with other non-seizure conditions.^{1,2} The specific FDA-approved indications for each of these agents are outlined in Table 1.³⁻⁴⁹ Seizure disorders can be organized into three major categories: generalized seizures, focal seizures, and unknown. Generalized seizures are subdivided into tonic-clonic (in any combination), absence, myoclonic, clonic, tonic, and atonic seizures types. Absence seizures are further divided into typical, atypical, and absence with special features (myoclonic absence, eyelid myoclonia) while myoclonic seizures are further divided into myoclonic, myoclonic atonic, and myoclonic. Epileptic spasms fall into the unknown seizure category. However, based on FDA-approved labeling, seizures are more commonly referred to as partial (or focal) seizures and generalized tonic-clonic seizures.⁵⁰

Pharmacologic management of epilepsy should be individualized, and focused on controlling seizures, avoiding treatment-related adverse events and maintaining or restoring quality of life. Prior to 1990, six major antiepileptic drugs were available for the treatment of various forms of epilepsy, including carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone (metabolized to phenobarbital) and valproic acid. Over the past two decades, many new chemical entities or formulations have become available in the United States. Some advantages of the newer antiepileptic drugs include more favorable adverse event profile, drug interaction profiles and ability to treat without the requirement of serum concentration monitoring.⁵¹⁻⁵³ Anticonvulsants are primarily used for their FDA-approved indications; however, in instances of severe and refractory seizure disorders, anticonvulsants may be used off-label for seizure types that are non-FDA approved. Currently there are several generic anticonvulsants available, and at least one generic agent is available within each anticonvulsant subclass.¹ Many anticonvulsants contained within this class review, such as pregabalin and lacosamide, are controlled substances. Anticonvulsants are available in a variety of formulations, which include: immediate release, delayed-release, and extended-release capsules or tablets; sprinkle capsules; chewable tablets; orally disintegrating tablets; solutions or suspensions; and injections.³⁻⁴⁹

Table 1. Current Medications Available in Therapeutic Class¹⁻⁴⁹

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Barbiturates			
Phenobarbital	Anticonvulsant (tablet), emergency control of certain acute convulsive episodes (injection), long term anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures (injection), treatment of generalized and partial seizures (elixir), hypnotic, for short term treatment of insomnia (injection), preanesthetic (injection), sedative	Elixir: 20 mg/5 mL Injection: 65 mg/mL 130 mg/mL Tablet: 15 mg 16.2 mg 30 mg 32.4 mg	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		60 mg 64.8 mg 97.2 mg 100 mg	
Primidone (Mysoline®*)	Control of grand mal, psychomotor, and focal epileptic seizures, used alone or concomitantly with other anticonvulsants	Tablet: 50 mg 250 mg	√
Benzodiazepines			
Clobazam (Onfi®)	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in patients two years of age or older	Tablet: 5 mg 10 mg 20 mg	-
Clonazepam (Klonopin®*)	Treatment of Lennox-Gastaut Syndrome (petit mal variant), akinetic, and myoclonic seizures, alone or as adjunct therapy, treatment of panic disorder, with or without agoraphobia	Orally disintegrating tablet: 0.125 mg 0.25 mg 0.5 mg 1 mg 2 mg Tablet: 0.5 mg 1 mg 2 mg	√
Diazepam (Diastat®*)	Management of selected, refractory, patients with epilepsy, on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity	Rectal gel: 2.5 mg 10 mg 20 mg	√
Hydantoins			
Ethotoin (Peganone®)	Control of generalized tonic-clonic and complex partial seizures	Tablet: 250 mg	-
Phenytoin (Phenytek®*, Dilantin®*)	Control of status epilepticus of the grand mal type (injection), control of generalized tonic-clonic and complex partial seizures (chewable tablet, extended-release capsule, suspension), prevention and treatment of seizures occurring during or following neurosurgery	Chewable tablet: 50 mg Extended-release capsule: 30 mg 100 mg 200 mg 300 mg Injection: 50 mg/mL Suspension: 125 mg/5 mL	√
Succinimides			
Ethosuximide	Control of absence epilepsy	Capsule:	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Zarontin ^{®*})		250 mg Syrup: 250 mg/5 mL	
Methsuximide (Celontin [®])	Control of absence seizures that are refractory to other drugs	Capsule: 300 mg	-
Anticonvulsants, Miscellaneous			
Brivaracetam (Briviact [®])	Adjunctive therapy in the treatment of partial seizures	Tablet: 10 mg 25 mg 50 mg 75 mg 100 mg Oral solution: 10 mg/mL Injection: 50 mg/5 mL	-
Carbamazepine (Carbatrol ^{®*} , Epitol ^{®*} , Equetro [®] , Tegretol ^{®*} , Tegretol XR ^{®*})	Generalized tonic-clonic seizures, mixed seizure patterns, partial seizures with complex symptomatology, acute treatment of manic or mixed episodes associated with bipolar disorder (Equetro [®]), trigeminal neuralgia	Chewable tablet: 100 mg Extended-release capsule: 100 mg 200 mg 300 mg Extended-release tablet: 100 mg 200 mg 400 mg Suspension: 100 mg/5 mL Tablet: 200 mg	√
Divalproex (Depakote ^{®*} , Depakote ER ^{®*})	Adjunctive therapy in patients with multiple seizure types, that include absence seizures (extended-release, delayed-release), monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures, acute treatment of the manic episodes associated with bipolar disorder (delayed-release), acute treatment of manic or mixed episodes associated with bipolar disorder (extended-release), prophylaxis of migraine headaches (extended-release, delayed-release)	Capsule (sprinkle): 125 mg Delayed-release tablet: 125 mg 250 mg 500 mg Extended-release tablet:	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		250 mg 500 mg	
Eslicarbazepine (Aptiom®)	Adjunctive treatment of partial-onset seizures	Tablet: 200 mg 400 mg 600 mg 800 mg	-
Ezogabine (Potiga®)	Adjunctive therapy in the treatment of partial onset seizures	Tablet: 50 mg 200 mg 300 mg 400 mg	-
Felbamate (Felbatol®*)	Patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use	Suspension: 600 mg/5 mL Tablet: 400 mg 600 mg	√
Gabapentin (Neurontin®*)	Adjunctive therapy in the treatment of partial seizures, postherpetic neuralgia	Capsule: 100 mg 300 mg 400 mg Solution: 250 mg/5 mL Tablet: 600 mg 800 mg	√
Lacosamide (Vimpat®)	Adjunctive therapy in the treatment of partial seizures	Injection: 200 mg/20 mL Solution: 10 mg/mL Tablet: 50 mg 100 mg 150 mg 200 mg	-
Lamotrigine (Lamictal®*, Lamictal CD®*, Lamictal ODT® Lamictal XR®*)	Adjunctive therapy in the treatment of partial seizures, adjunctive therapy in the treatment of primary generalized tonic-clonic seizures, adjunctive therapy for seizures associated with Lennox–Gastaut syndrome (chewable and orally disintegrating tablets), monotherapy in patients with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as the single antiepileptic drugs, maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients	Chewable tablet: 2 mg 5 mg 25 mg Extended-release tablet: 25 mg 50 mg 100 mg 200 mg 250 mg	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	treated for acute mood episodes with standard therapy (chewable and orally disintegrating tablets)	300 mg Orally disintegrating tablet: 25 mg 50 mg 100 mg 200 mg Tablet: 25 mg 50 mg 100 mg 150 mg 200 mg 250 mg	
Levetiracetam (Elevsia XR [®] , Keppra ^{®*} , Keppra XR ^{®*})	Adjunctive therapy in the treatment of myoclonic seizures in patients with juvenile myoclonic epilepsy (injection, tablets), adjunctive therapy in the treatment of partial seizures, adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (injection, tablets),	Extended-release tablet: 500 mg 750 mg Extended-release tablet (Elevsia XR [®]): 1,000 mg 1,500 mg Injection: 500 mg/5 mL Solution: 100 mg/mL Tablet: 250 mg 500 mg 750 mg 1,000 mg	√
Oxcarbazepine (Oxtellar XR [®] , Trileptal ^{®*})	Monotherapy and adjunctive therapy in the treatment of partial seizures	Extended-release tablet: 150 mg 300 mg 600 mg Suspension: 300 mg/5 mL Tablet: 150 mg 300 mg 600 mg	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Perampanel (Fycompa®)	Adjunctive therapy in the treatment of partial onset seizures†	Tablet: 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg	-
Pregabalin (Lyrica®)	Adjunctive therapy in the treatment of partial seizures, fibromyalgia, neuropathic pain associated with diabetic peripheral neuropathy, neuropathic pain associated with spinal cord injury, postherpetic neuralgia	Capsule: 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 225 mg 300 mg Solution: 20 mg/mL	-
Rufinamide (Banzel®)	Adjunctive therapy for seizures associated with Lennox–Gastaut syndrome	Suspension: 40 mg/mL Tablet: 200 mg 400 mg	-
Tiagabine (Gabitril®*)	Adjunctive therapy in the treatment of partial seizures	Tablet: 2 mg 4 mg 12 mg 16 mg	√
Topiramate (Qudexy XR®, Topamax®*, Trokendi XR®)	Adjunctive therapy in patients with partial onset or primary generalized tonic-clonic seizures, adjunctive therapy for seizures associated with Lennox–Gastaut syndrome, monotherapy (initial) in patients with partial onset or primary generalized tonic-clonic seizures, prophylaxis of migraine headaches	Capsule (sprinkle): 15 mg 25 mg Tablet: 25 mg 50 mg 100 mg 200 mg Extended-release capsule: 25 mg 50 mg 100 mg 150 mg 200 mg	√
Valproic acid (Depakene®*, Stavzor®)	Adjunctive therapy in patients with multiple seizure types, that include absence seizures, monotherapy and adjunctive therapy of complex partial seizures and simple and	Capsule: 250 mg Delayed-	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	complex absence seizures, acute treatment of the manic episodes associated with bipolar disorder (delayed-release), prophylaxis of migraine headaches (delayed-release)	release capsule: 125 mg 250 mg 500 mg Solution: 250 mg/5 mL	
Vigabatrin (Sabril®)	Adjunctive therapy for adult patients with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss (tablet), monotherapy for pediatric patients (one month to two years of age) with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss (solution)	Solution (powder): 500 mg Tablet: 500 mg	-
Zonisamide (Zonegran®*)	Adjunctive therapy in the treatment of partial seizures	Capsule: 25 mg 50 mg 100 mg	√

*Generic available in at least one dosage form or strength.

†With or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

Evidence-based Medicine

- The safety and efficacy of anticonvulsants, as monotherapy and as adjunct therapy, have been evaluated in numerous clinical trials for their respective FDA-approved indications. Selected trials have evaluated the use of anticonvulsants for the treatment of various seizures disorders as well as non-seizure disorders.⁵⁴⁻¹⁹⁸
- The safety and efficacy of Elepsia XR® (levetiracetam extended-release tablets) was established based on the clinical trials used to approve Keppra ER® (levetiracetam extended-release tablets).^{20,49}
- Hancock et al conducted a meta-analysis of 14 randomized controlled trials which included infants and children with infantile spasms. Treatment with vigabatrin was associated with a complete cessation of spasms in 7/20 (35%) patients compared to 2/20 (10%) patients treated with placebo. A >70% reduction in the number of spasms was reported in 40% of patients treated with vigabatrin compared to 15% of patients treated with placebo.⁵⁵
- Another meta-analysis by Hancock et al included trials that evaluated the safety and efficacy of felbamate, lamotrigine, rufinamide and topiramate in the treatment of Lennox-Gastaut Syndrome (LGS). While all of these agents demonstrated some efficacy, the optimum treatment of LGS remained uncertain as no single drug was highly efficacious. Felbamate, lamotrigine, rufinamide and topiramate may be helpful as add-on therapy.¹⁴⁵
- The results of a study by Ng et al demonstrated that the mean percent reduction in weekly drop seizures was 41.2% with clobazam 0.25 mg/kg/day (P=0.0120), 49.4% with clobazam 0.5 mg/kg/day (P=0.0015) and 68.3% with clobazam 1.0 mg/kg/day (P<0.0001) compared to 12.1% for placebo.¹²⁵
- In a study by Porter et al, treatment with ezogabine 600, 900 and 1,200 mg reduced the total monthly seizure frequency from baseline by 23, 29 and 35% compared to 13% with placebo (P<0.001 for all).⁵⁵ In a second study of patients with drug-resistant partial epilepsy, ezogabine 1,200 mg daily reduced the total monthly seizure frequency from baseline by 44.3% compared to 17.5% with placebo (P<0.001).⁷⁰
- Perampanel is approved as adjunctive therapy in patients with partial onset seizures. In one study perampanel 8 or 12 mg significantly reduced seizure frequency compared to placebo (P=0.0261 and P=0.0158 for 8 and 12 mg, respectively); however, there was no significant difference in the

proportion of patients who achieved a seizure reduction >50% from baseline compared to the placebo group.⁸⁷ Similar results were reported in a second study (P<0.001 and P=0.011 for 8 and 12 mg, respectively); however, more patients treated with perampanel 8 or 12 mg had a reduced seizure frequency >50% from baseline compared to placebo (P=0.002 and P<0.001 for 8 and 12 mg, respectively).⁸⁸ In a third study, treatment with perampanel 4 or 8 mg significantly reduced seizure frequency compared to placebo (P=0.003 and P<0.001 for 4 mg and 8 mg, respectively). Moreover, a greater proportion of patients treated with perampanel 4 or 8 mg achieved a reduction in seizure frequency >50% from baseline compared to placebo (P=0.013 and P<0.001 for 4 and 8 mg, respectively).⁸⁹

- Eslicarbazepine was evaluated in three double-blind, multi-center, randomized, placebo-controlled trials. Each of these trials compared adjunctive treatment with eslicarbazepine to placebo in patients who were currently receiving one to three anti-epileptic drugs. In the first and second published trials, the investigators compared eslicarbazepine at a dose of 400, 800 and 1,200 mg once daily to placebo for 12 weeks.^{64,65} In a pooled analysis of the three studies (third trial has not been published), the primary endpoint of seizure frequency per four weeks was 7.7 in the placebo group (N=406) compared to 7.3 with eslicarbazepine 400 mg (N=185; P=0.8136), 6.1 with 800 mg (N=375; P=0.0001) and 5.7 with 1,200 mg (N=352; P<0.0001). The proportion of patients who achieved a seizure reduction of at least 50% from baseline was 20.9% in the placebo group compared to 22.2% with eslicarbazepine 400 mg, 32.3% with 800 mg and 40.9% with 1,200 mg.⁶⁴⁻⁶⁶ A fourth double-blind, multi-center, randomized, placebo-controlled trial compared adjunctive treatment with eslicarbazepine to placebo in patients who were currently receiving one to two anti-epileptic drugs. Investigators compared eslicarbazepine at a dose of 800 and 1,200 mg once daily to placebo for 12 weeks. The primary endpoint of seizure frequency per four weeks was 7.3 in the placebo group (N=88) compared to 5.7 with eslicarbazepine 800 mg (N=85; P=0.048) and 5.5 with 1,200 mg (N=80; P=0.021). The proportion of patients who achieved a seizure reduction of at least 50% from baseline was 22.6% in the placebo group compared to 34.5% with eslicarbazepine 800 mg (P=0.106) and 37.7% with 1,200 mg (P=0.020).⁶⁷

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - The 2012 National Institute for Clinical Excellence guideline recommends carbamazepine and lamotrigine as first-line treatment of children, young people, and adults with newly diagnosed focal seizures (partial seizures). Levetiracetam, oxcarbazepine or sodium valproate should be offered if first-line therapies prove inadequate, and adjunctive therapy should be considered if a second well-tolerated antiepileptic also proves inadequate. Sodium valproate is recommended first-line for the treatment of children, young people, and adults with newly diagnosed generalized tonic-clonic focal seizures. Lamotrigine should be offered if sodium valproate proves inadequate, and carbamazepine and oxcarbazepine should be considered. Adjunctive therapy with clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate should be offered to all patients if first-line therapies are inadequate.¹⁹⁹
 - Vigabatrin (oral solution) is Food and Drug Administration (FDA)-approved for the management of infantile spasm. According to the 2012 American Academy of Neurology medical management of infantile spasms guideline, there is insufficient evidence to support the use of agents other than adrenocorticotropic hormone and vigabatrin. Evidence suggests that adrenocorticotropic hormone may be preferred over vigabatrin for short-term management.²⁰⁰
 - Clobazam, clonazepam, lamotrigine, rufinamide and topiramate are FDA-approved for the management of Lennox Gastaut Syndrome. Sodium valproate is recognized as first-line, with lamotrigine recommended as adjunctive therapy if needed.¹⁹⁹
 - Treatment guidelines recommend valproate and carbamazepine as potential beneficial options for the management of adults with a manic or mixed bipolar episode. Lamotrigine, topiramate, or gabapentin are unlikely beneficial in this clinical situation and oxcarbazepine may be considered for treatment. With regard to bipolar depression in adults, lamotrigine should be considered as a potential first-line option, and patients who do not respond to initial monotherapy should receive combination therapy with lithium.²⁰¹⁻²⁰⁵

- o Divalproex, topiramate and valproic acid are FDA-approved for the prophylaxis of migraine headaches, and all should be offered for migraine prevention according to the 2012 guidelines from the American Academy of Neurology/American Headache Society. Furthermore, carbamazepine may be considered for migraine prevention as it is a possibly effective treatment, and lamotrigine is ineffective.²⁰⁶
- o According to the American Academy of Neurology, anticonvulsants, antidepressants, opioids and other pharmacologic agents (capsaicin, isosorbide dinitrate spray, and lidocaine patch) are potential treatment options for painful diabetic neuropathy. If clinically appropriate, pregabalin should be offered for treatment. Gabapentin and sodium valproate are other anticonvulsants that should be considered for treatment.²⁰⁷
- o According to the American Academy of Neurology, first-line therapies for the management of postherpetic neuralgia include tricyclic antidepressants, gabapentin, pregabalin, opioids, and topical lidocaine. At this time the use of these therapies for long-term management remains uncertain.²⁰⁸
- o The use of anticonvulsants in the management of fibromyalgia is not addressed in the European League Against Rheumatism guidelines.²⁰⁹
- Other Key Facts:
 - o The majority of anticonvulsants are available in a generic formulation, and there is at least one generic agent available within each pharmacologic class.
 - o Clobazam was approved by the FDA in 2011; however, this agent has been available internationally for several years for the treatment of anxiety and epilepsy.
 - o Ezogabine has a unique mechanism of action in that it may act as an anticonvulsant by reducing excitability through the stabilization of neuronal potassium channels in an “open” position.³⁵
 - o Perampanel is a first-in-class anticonvulsant that works as a highly selective, non-competitive AMPA-type glutamate receptor antagonist.²¹⁰
 - o The most recently FDA-approved anticonvulsant, eslicarbazepine, provides for another treatment option for patients with partial-onset seizures.

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