

MTF Formulary Management for Anticonvulsant and Anti-Mania Agents
 Defense Health Agency Pharmacy Operations Division

Bottom Line

- No anticonvulsant or anti-mania agents are designated nonformulary.
- There are no changes to the Basic Core Formulary drugs.
- The manual prior authorization for topiramate ER (Trokendi XR and Qudexy XR) limits use to FDA-approved indications; there were no changes to the prior authorization criteria since implementation in December 2015.
- No antiepileptic drug has proven superior overall at treating seizures. When used for the appropriate seizure type, the newer antiepileptic drugs are roughly equivalent in efficacy.
- Antiepileptic treatment selection should be based on drug characteristics, including side effect profile, ease of administration, and potential drug interactions, as well as patient characteristics, including seizure type and epilepsy syndrome.

Uniform Formulary (UF) Decision: The Director, DHA, approved the recommendations from the May 2016 DoD P&T Committee meeting on July 28, 2016.

Basic Core Formulary (BCF)		
MTFs <u>must</u> have on formulary	MTFs <u>may</u> have on formulary	MTFs <u>must not</u> have on formulary
<ul style="list-style-type: none"> • carbamazepine IR tablets, chewable tablets, oral suspension (Tegretol, generics) • carbamazepine ER tablets (Tegretol XR, generics) • divalproex (Depakote, Depakote ER, Depakote Sprinkles) • phenytoin ER capsules, chewable tablets, oral suspension (Dilantin, Dilantin-125, generics) • phenobarbital 	<ul style="list-style-type: none"> • carbamazepine ER (Tegretol XR, Carbatrol, generics; Equetro XR) • clobazam (Onfi) • eslicarbazepine (Aptiom) • ethosuximide (Zarontin, generics) • felbamate (Felbatol, generics) • lacosamide (Vimpat) • lamotrigine IR, ER, and chewable tablets (Lamictal, Lamictal XR, Lamictal CD, generics) • lamotrigine orally dissolving tablets (Lamictal ODT) • levetiracetam IR, ER, and chewable tablets (Keppra, Keppra XR, generics) • oxcarbazepine (Trileptal, generics) • oxcarbazepine XR (Oxtellar XR) • perampanel (Fycompa) • primidone (Mysoline, generics) • rufinamide (Banzel) • topiramate IR and sprinkle (Topamax, Topamax Sprinkle, generics) • topiramate ER (Trokendi XR) • topiramate ER (Qudexy XR) • valproic acid (Depakene, generics) • vigabatrin (Sabril) • zonisamide (Zonegran, generics) 	<ul style="list-style-type: none"> • None

Formulary Management Issues

- The Anticonvulsant and Anti-Mania Drug Class has not been previously reviewed. Prior to implementation of the UF Rule in 2005, several drugs in the class were designated as Basic Core Formulary (BCF).
- There are over 40 antiepileptic drugs (AEDs) available in the United States. Most are available in generic formulations, and several products now have extended release (ER) versions. Generic formulations of levetiracetam ER (Keppra XR) and lamotrigine ER (Lamictal XR) recently entered the market. Brivaracetam (Briviact) is a new product that will be reviewed as an innovator drug at an upcoming DoD P&T Committee meeting.
- Five of the AEDs are unique, branded products with no generic or therapeutic equivalents: lacosamide (Vimpat), perampanel (Fycompa), clobazam (Onfi), vigabatrin (Sabril), and rufinamide (Banzel).
- Five other products are branded formulations with therapeutic alternatives: topiramate ER (Trokendi XR and Qudexy XR), oxcarbazepine (Oxtellar XR), eslicarbazepine (Aptiom), and carbamazepine ER (Equetro ER). Brief clinical summaries of the branded products are included below.
- The older generic AEDs and anti-mania drugs were not a focus of the clinical and cost reviews and included the following products: phenobarbital, primidone (also used for essential tremor), felbamate, and ethosuximide (the drug of choice for absence seizures). These products will remain designated as formulary on the UF. Tiagabine (Gabitril, generic) and ezogabine (Potiga) are GABA-type drugs used for seizures; they are classified as part of the Antidepressants/Non-Opioid Pain Drug Class and were not reviewed.

Carbamazepine (Tegretol), Carbamazepine ER (Equetro XR)

- Carbamazepine (Tegretol) is available in generic formulations and approved for patients as young as six years old. The branded carbamazepine product, Equetro ER, is only approved for mania and not seizures, and does not have clinically compelling advantages over generic carbamazepine formulations.

Oxcarbazepine (Trileptal), Oxcarbazepine ER (Oxtellar XR), Eslicarbazepine (Aptiom)

- Oxcarbazepine (Trileptal) is available in generic formulations and approved for pediatric patients down to the age of two years with partial seizures. It is available in a liquid formulation. The branded products Oxtellar XR and eslicarbazepine (Aptiom) are dosed once daily, and only offer a convenience to the patient.

Topiramate IR and ER (Topamax, generic; Trokendi XR, Qudexy XR)

- Topiramate immediate release (IR) has several off-label uses including weight loss, bipolar disorder, alcohol dependency, obsessive compulsive disorder, and post-traumatic stress disorder. In addition to partial onset seizures and primary generalized tonic-clonic seizures, topiramate IR is approved for patients with Lennox-Gastaut seizures down to the age of two years old. It is also approved for migraine headache.
- The newer topiramate ER products, Trokendi XR and Qudexy XR, do not offer clinically compelling advantages over generic topiramate IR. Qudexy XR does have data in patients with G-tubes, but this information is not included in the package insert. Topiramate ER is an “authorized generic” formulation made by the manufacturer of Qudexy XR.

Clobazam (Onfi)

- Clobazam (Onfi) is approved as adjunctive therapy for Lennox-Gastaut seizures in patients as young as two years old. The compound causes less sedation than typical benzodiazepines due to receptor selectivity. It is frequently used in pediatric patients with refractory seizures.

Lacosamide (Vimpat)

- Lacosamide (Vimpat) has a unique mechanism of action at the sodium channels, is well tolerated except for dizziness and somnolence, is easy to titrate, and is approved for partial onset seizures in patients down to age 17. An oral solution and tablets are available.

Perampanel (Fycompa)

- Perampanel (Fycompa) has a unique mechanism of action at the glutamate receptor. Its place in therapy is for refractory patients with secondary generalized seizures or exclusively for focal seizures as a second- or third-line agent. Fycompa is the only AED with a black box warning for hostility, aggression, and homicidal ideation. Its long duration of action can prolong adverse effects of sedation, headache, and dizziness.

Rufinamide (Banzel)

- Rufinamide (Banzel) is approved for Lennox-Gastaut seizures in children down to the age of one year. There are concerns of shortened QT interval and risk of inducing status epilepticus.

Vigabatrin (Sabril)

- Vigabatrin (Sabril) is approved for infantile spasms in patients down to the age of one year old. Sabril is also approved for refractory complex partial seizures in patients as young as 10 years of age. The risk of vision loss associated with Sabril requires restricted distribution and enrollment in a patient registry.

Safety and Tolerability

- In terms of safety, since clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a particular AED cannot be directly compared to rates reported in the clinical trials of another drug, and may not reflect the rates observed in practice.
- While each AED may have characteristic adverse events, most cause dizziness, somnolence, and fatigue.

Summary

- No AED has proven superior overall at treating seizures. When used for the appropriate seizure type, the newer AEDs are roughly equivalent in efficacy.
- Clinical guidelines indicate that a variety of medications are required to treat seizures effectively.
- AED treatment selection should be based on drug characteristics, including side effect profile, ease of administration, and potential drug interactions, as well as patient characteristics, including seizure type and epilepsy syndrome.

Prior Authorization for Topiramate ER (Trokendi XR and Qudexy XR)

- Manual prior authorization criteria limit the use of Qudexy XR and Trokendi XR to the FDA-approved indications for seizures and appropriate age ranges. Patients are required to try generic topiramate IR first, unless there is a contraindication or adverse reaction with the generic product.

References

- DoD P&T Committee minutes: <http://www.health.mil/PandT>
- Current/future drug classes under review by the DoD P&T Committee <http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-PT-Committee>
- TRICARE Formulary Search Tool: <http://www.health.mil/formulary>
- Prior Authorization/Medical Necessity forms: See Formulary Search Tool above.
- Formulary Management Documents (including this one) available at: <http://www.health.mil/DoDPTResources>
- Point of contact for additional information: dha.jbsa.pharmacy.list.poduf@mail.mil

Anticonvulsant and Anti-Mania Agents BRANDED products MTF Dose/Price Comparison	
Drug	MTF Avg Cost/Day (May 2016)
Basic Core Formulary	
Generic formulations	\$ = Most Cost-Effective
Uniform Formulary	
carbamazepine ER (Equetro)	\$\$ = Less Cost-Effective
oxcarbazepine ER (Oxtellar XR)	
levetiracetam (Keppra XR)*	
lacosamide (Vimpat)	
topiramate ER (Qudexy XR authorized generic)	
topiramate ER (Trokendi XR)	\$\$\$ = Less Cost Effective
perampanel (Fycompa)	
topiramate ER (Qudexy XR)	
clobazam (Onfi)	
eslicarbazepine (Aptiom)	
lamotrigine ER (Lamictal XR)*	\$\$\$\$ Least Cost Effective
vigabatrin (Sabril)	
Legend: \$ = "Most Cost-Effective" represents Rx's with the <u>lowest cost</u> and best clinical efficacy \$\$ = "Less Cost-Effective" represents <u>higher cost</u> Rx's with similar clinical efficacy \$\$\$ = "Less Cost-Effective" represents <u>next higher cost</u> Rx's with similar clinical efficacy \$\$\$\$ = "Least Cost-Effective" represents Rx's with the <u>highest cost</u> with similar clinical efficacy	
*Recent generic entrants for Keppra XR and Lamictal XR will result in price reductions	