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Drug Class Update with New Drug Evaluation: Antiepileptics (non-injectable)

Date of Review: October 2022

Generic Name: ganaxolone

Date of Last Review: Oct 2021
Dates of Literature Search: 07/30/2021 - 07/31/2022
Brand Name (Manufacturer): Ztalmy® (Marinus)
Dossier Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary: Is there any new evidence that would change the current policy for medicines to treat seizures?

- National Institute for Health and Care Excellence (NICE) recommend many different medicines to treat seizures.
  - Guidelines from NICE recommend medicines based on the type of seizure and the person's specific situation.
  - Most recommendations include use of one medicine at a time. But if seizures are not controlled, then more than one medicine may be prescribed by a provider.
- Ganaxolone is a new medicine the Food and Drug Administration (FDA) approved to treat a rare type of seizures, called cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD). One small study lasting 17 weeks showed that adding this medicine decreased the number of seizures by 27% compared to patients who did not take ganaxolone. People were included in the study if:
  - they were at least 2 years old, and
  - had already tried taking other medicines for seizures, and
  - continue taking their current doses of other medicines for seizures while taking ganaxolone.
- Medicaid Open Card will pay for medicines that are most often used as the first seizure treatment when prescribed by a provider. Providers must explain to the Oregon Health Authority why someone needs other medicines for seizures. This process is called prior authorization.
- The Drug Use Research Management program does not recommend any changes to this policy.

Purpose for Class Update:
To define place in therapy for the new antiepileptic drug (AED), ganaxolone, recently approved with orphan drug status by the Food and Drug Administration (FDA) for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older. In addition, new comparative evidence for antiepileptic agents used in management of seizures will be reviewed.[1,2]

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Research Questions:

1. Is there new comparative evidence that AEDs differ in efficacy or harms for management of seizures?
2. What is the effectiveness of ganaxolone in reducing seizures in people with CDD?
3. What is the comparative harms of ganaxolone in people with CDD?
4. Are there certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) in which ganaxolone may be beneficial or cause more harm?

Conclusions:

- Since the last AED update, one high-quality guideline has been published. National Institute for Health and Care Excellence (NICE) issued guidelines for treatment of epilepsy in children, young people, and adults.[3] Recommendations **(table 1)** align with current preferred drug list (PDL) and prior authorization (PA) polices.
- There is low quality evidence that ganaxolone reduces the percentage of seizures during a 28-day period as add-on therapy compared to placebo in patients with CDD experiencing at least 16 major motor seizures per 28 days, who are taking up to 4 other AEDs, and have failed appropriate trials of at least 2 AEDs (median change: ganaxolone -30.7%, interquartile range [IQR] -49.5 to -1.9%; placebo -6.9%, IQR -24.1% to 39.7 %; difference -27.1%, 95% confidence interval [CI] -47.9 to -9.6).[4,5] Evidence derives from results of a single, small, fair quality trial with concerns for unclear risk of bias and inconsistency.
- There is insufficient evidence evaluating efficacy and safety for the use of ganaxolone for seizure disorders other than CDD and in adults with drug-resistant partial-onset seizures.
- The most common treatment emergent adverse event (TEAE) was sedation (ganaxolone 36% vs. placebo 16%), which may be additive with other sedating medications. Most serious TEAEs were unlikely to be related to ganaxolone and there were no deaths and few discontinuations due to TEAE (ganaxolone 4% vs. placebo 8%).[5]
- There is insufficient safety and efficacy data on ganaxolone with long-term use and in those under 2 years old. The racial and ethnic make-up of this study is not representative of the general or Medicaid population, it is unclear if this is due to disease epidemiology or reduced access to testing and diagnosis of this rare disease.

Recommendations:

- Recommend ganaxolone be voluntary non-preferred and implement safety edit to restrict to FDA approved indication and dose.
- Recommend change class name to “Antiepileptics, Outpatient” and include new autoinjector formulation of midazolam as non-preferred.
- No other change to PDL recommended based on clinical information.
- After review of costs in executive session, midazolam spray (NAYZILAM) and diazepam spray (VALTOCO) were made preferred products.

Summary of Prior Reviews and Current Policy

- Current PDL placement for agents listed in **Appendix 1**.
- Certain agents in this class fall within medication carve-out for mental health medications and may have a “preferred” or “voluntary non-preferred” status.
- Current PA policies for cannabidiol, clobazam, fenfluramine, pregabalin, stiripentol, and topiramate are available in **Appendix 5**.
- Class was most recently reviewed in Oct 2021 with inclusion of 5 high-quality systematic reviews and no new guidelines. No changes were made to PA or PDL.

Background:

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) results from gene mutations on the short arm of the X-chromosome and was previously thought to be an early onset variant of Rett Syndrome.[6] These mutations are typically *de novo* and present in an estimated 1 in 40,000 to 60,000 live births. Genetic testing for the disorder is becoming more common.[2] Females with CDD are 4-fold more common than males; it is hypothesized that a CDKL5 mutation is often lethal in male fetuses.[6] Seizures are often the first symptom of CDD, and 90% experience their first seizure in the first 3 months of life, and 96.9% in the first 6 months.[6] An estimated 8-16% of females with early-onset epilepsy have a CDKL5 mutation, as well as 28% of females and 5.4% of males with early infantile epileptic encephalopathy.[6]

Seizures in patients with CDD are often refractory. Other symptoms include hypotonia, psychomotor developmental disorders, intellectual disability, and cortical vision disorders.[6] Patients with mild cases are less common, though these patients can walk, use simple sentences, and may be able to control seizures with drug therapy.[6] Severe forms are often unresponsive to drug therapy and may have microcephaly as well as other severe complications.[6] Roughly 66% of females and 35% of males can sit unsupported, and 25% of females can stand. Almost all patients have normal head circumference at birth, but 44.4% may fall below the 3rd percentile as early as 2 years.[6] Patients with CDD may experience difference seizure types and drug therapy is targeted to type.[2,6] Drug resistance is common. Patients may also be diagnosed with Lennox Gastaut syndrome or West syndrome based on seizure semiology.[2] There were no previously approved AEDs for CDD, though levetiracetam, topiramate, clobazam, and phenobarbital were the most frequently prescribed off-label.[2] Cannabis derivatives, including cannabidiol (EPIDIOLEX), have also been used based off-label in a small number of individuals, though high-quality efficacy data are lacking and 29% experienced seizure worsening.[2]

Expert opinion is often used to define minimum clinically important difference (MCID) thresholds for seizure reduction in epilepsy. There are variations among experts and in type of seizure disorder. NICE discussed a 30% reduction in seizure frequency as the minimum to continue treatment in Dravet syndrome, while a 50% reduction would be a clearer indication of benefit.[7] The FDA noted that a 50% reduction in frequency responder analysis did not align with median seizure frequency change primary endpoint in the medication under review for CDD, and that a 25% responder rate supports the biologic effect of seizures in CDD. [2]

There were fewer than 5 patients identified in the Fee-for-Service population with CDD.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 83 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

A systematic review and meta-analysis was
New Guidelines:
High Quality Guidelines:

NICE[3]
In April 2022, National Institute for Health and Care Excellence provided guidance for epilepsies in children, young people, and adults. Recommendations for first and second line monotherapy and add-on treatment are summarized in **table 1**. Updated recommendations from a July 2022 technical appraisal report are also included.[7] Certain AED agents may exacerbate specific seizure types, and recommendations may change for patients experiencing multiple seizure types.[3] General recommendations include use of monotherapy whenever possible, and when monotherapy is unsuccessful, to carefully cross taper to attempt monotherapy with another AED.[3] Attempt add-on therapy if monotherapy is unsuccessful.[3] Treatment for epilepsy should be individualized.[3] Non-pharmacologic therapies (e.g. ketogenic diet) are included in NICE guidance though omitted as beyond the scope of this class update.

Table 1. Treatment recommendations[3]

Seizure Type	Treatment Recommendation	Population (if applicable)
Generalized Tonic-Clonic	First line monotherapy: sodium valproate	• Boys and men • Girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children • Women who are unable to have children
	First line monotherapy: lamotrigine or levetiracetam	• Women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children).
	Add-on treatment (first-line): Clobazam, lamotrigine, levetiracetam, perampanel, sodium valproate*, topiramate.	NA
	Add-on treatment (second-line): brivaracetam, lacosamide, phenobarbital, primidone, zonisamide	
Focal Seizures with or without evolution to bilateral tonic-clonic seizures	First line monotherapy: lamotrigine or levetiracetam	NA
	Second line monotherapy: carbamazepine, oxcarbazepine, zonisamide	
	Third line monotherapy: lacosamide	
	Add-on treatment: carbamazepine, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate, zonisamide.	
Absence seizures	First line monotherapy: ethosuximide	NA
	Second line monotherapy or add on: sodium valproate	• Boys and men • Girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children • Women who are unable to have children

	Second line monotherapy or add on: lamotrigine or levetiracetam	NA
Myoclonic seizures	First line monotherapy: sodium valproate	• Boys and men • Girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children • Women who are unable to have children
	First line monotherapy: levetiracetam	• Women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children).
	Second line monotherapy or add on: levetiracetam	NA
Tonic or atonic seizures	First line monotherapy: sodium valproate	• Boys and men • Girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children • Women who are unable to have children
	First line monotherapy: lamotrigine	• Women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children).
	Second line monotherapy or add on: lamotrigine	NA
Idiopathic generalized epilepsies	First line monotherapy: sodium valproate	• Boys and men • Girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children • Women who are unable to have children
	First line monotherapy: lamotrigine or levetiracetam	• Women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children).
	Second line monotherapy or add on: lamotrigine or levetiracetam	NA
Dravet Syndrome[7]	First line monotherapy: sodium valproate	• Use with caution in women and girls, but recommended first-line due to disease severity and lack of other effective first line treatments.
	First line add-on: stiripentol and clobazam	• Triple therapy • Stiripentol may be used alone as first add on, or as second add-on if clobazam already added to sodium valproate.[7]
	Second line add-on: consider cannabidiol in combination with clobazam	• Consider only for people age 2 years and over.
	Second line add-on: fenfluramine[7]	NA
Lennox-Gastaut Syndrome	First line monotherapy: sodium valproate	• Use with caution in women and girls, but recommended first-line due to disease severity and lack of other effective first line treatments.
	Second line monotherapy or add on: lamotrigine	NA
Infantile Spasms Syndrome	First line combination: high dose prednisolone and vigabatrin	• If not due to tuberous sclerosis, and child not at high risk of steroid-related side effects. Consider vigabatrin alone.

	Second line monotherapy or add-on: levetiracetam, nitrazepam (not available in United States), sodium valproate, topiramate, non-pharmacologic therapies.	NA
Self-limited Epilepsy with Centrotemporal Spikes	First line monotherapy: lamotrigine or levetiracetam	• If unsuccessful, try the other of these options.
	Second line monotherapy: carbamazepine, oxcarbazepine, zonisamide	NA
Epilepsy with myoclonic-atonic seizures (Doose Syndrome)	First line monotherapy: levetiracetam or sodium valproate	• If unsuccessful, try the other of these options.
	Second line monotherapy or add on: consider non-pharmacologic therapy	NA
Status epilepticus (community settings)	If patient has individualized emergency management plan, administer medication according to plan	NA
	First line in community settings: Give benzodiazepine (buccal midazolam [formulation available in United Kingdom] or rectal diazepam) immediately	• If seizure does not stop within 5 to 10 minutes, call emergency services and give second dose if available.
*Except in women and girls able to have children NA = not applicable		

After review, 2 guidelines were excluded for quality and topic focus, and 1[8] was excluded because recommendations were included in later publication by the same organization.

New Formulations or Indications:
Zonisamide (ZONISADE) was approved in July 2022 as a new 100 mg/5mL suspension formulation for the treatment of partial-onset seizures in adults and pediatric patients 16 years and older.[9] Zonisamide received initial U.S. approval in 2000[9] and is also available generically as 25 mg, 50 mg, and 100 mg capsules.

Midazolam autoinjector for intramuscular use was approved in August 2022 for treatment of status epilepticus in adults. Approval was based on an active control, double-blind, double-dummy trial (N=893) of 10 mg intramuscular midazolam (using a different autoinjector) to 4 mg intravenous lorazepam administered by paramedics, with the endpoint of termination of convulsive seizure activity prior to arrival at emergency department (midazolam 73.4% vs. lorazepam 63.4%; p=0.002). Additionally, approval was based on pharmacokinetic comparison of this midazolam autoinjector to midazolam vial in healthy adults. It carries same black box warnings of other benzodiazepines for risks of concomitant use with opioids; abuse, misuse, and addiction; and dependence and withdrawal reactions. Continuous monitoring of respiratory and cardiac function is recommended.[10]

Stiripentol (DIACOMIT) received an expanded indication in July 2022 for the treatment of Dravet syndrome in patient taking clobazam who are 6 months of age and older and weighing at least 7 kg.[11] The previous indication included patients 2 years and older. There is no evidence to support monotherapy.

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts[12]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Ethosuximide	Zarontin	10/2021	Warnings and Precautions	Addition of drug-induced immune thrombocytopenia

Topiramate	Multiple	1/2022	Warnings and Precautions	Addition of decrease in bone mineral density and negative effects on growth (height and weight)

Randomized Controlled Trials:
A total of 222 citations were manually reviewed and excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). An additional 41 citations (trials and systematic reviews) were excluded for a publication date prior to July 30, 2021 (search end date from previous literature scan presented in Oct 2021).

NEW DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Ganaxolone (ZTALMY) is a neuroactive steroid gamma-aminobutyric acid A ($GABA_A$) receptor positive modulator which received FDA approval in March 2022 for treatment of CDD in patients 2 years and older.[1] It has a controlled substance classification of schedule V from the Drug Enforcement Agency (DEA).

Ganaxolone was evaluated in a single, double-blind, randomized, placebo-controlled, multicenter trial enrolling patients aged 2 to 21 years with a pathogenic or possibly pathogenic CDKL5 variant and at least 16 major motor seizures during both 4-week periods within a historical 8-week period and were taking up to 4 concomitant AEDs at stable doses for 1 month.[5] Major motor seizures included bilateral tonic, generalized tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic.[5] Those meeting criteria entered a 6-week baseline period, then were randomized to adjunctive treatment with enteral ganaxolone or matching placebo. Those with various other neurological conditions, abnormal liver function, considerable renal insufficiency, or on non-AED interacting medications were excluded.[4,5] Detailed inclusion and exclusion are included in **table 5**. After randomization, a weekly weight-based titration of study agents occurred over 4 weeks, followed 13 weeks of maintenance dosing.[5] If the patient weighed 28 kg or less, the medication was initiated at 6 mg/kg/**dose** and titrated to a maximum of 21 mg/kg/**dose**, given three times a day.[5] Those over 28 kg started 150 mg three times daily and were titrated to a maximum dose of 600 mg three times daily.[5] Daily seizure frequency and type were assessed by the patient's caregiver and entered into a daily electronic diary.[5] The primary efficacy endpoint was percentage change in major motor seizure frequency at week 17 compared to the 6-week baseline period.[5] Participants were primarily female (79%) and either White (92%) or Asian (5%). The population included a small proportion of Hispanic/Latino participants (9.9%) and the median age was 6 years (IQR 3-11 years).[5]

The median percentage change in 28-day major motor seizure frequency from baseline to week 17 was greater in the ganaxolone group (-30.7%; IQR -49.5 to -1.9) when compared to placebo (-6.9%; IQR -24.1 to 39.7).[5] The difference in changes between groups was -27.1% (95% CI -47.9 to -6.6%; p=0.0036).[5]

Bias was low to unclear. While the overall population studied was small (n=101), baseline characteristics related to demographics were generally balanced. There were differences in seizure type and frequencies **(table 5)** between groups, with ganaxolone patients having a higher median and IQR for baseline

seizures. Baseline use of AEDs was similar (within 5%) for most of the 23 agents reported.[2] Lamotrigine use was less common in the ganaxolone group (6% vs. 12%) and while oxcarbazepine was more common (6% vs. 0%) when compared to placebo. These were only the 9th and 10th most frequently used AED and unlikely to affect overall findings.[5] Caregiver training and consistency related to assessment of frequency and type of seizures was not described.[4,5] Additionally, sedation from ganaxolone use in some patients could potentially result in unblinding. Ganaxolone use for drug-resistant partial-seizures in the adult population (n=405) was studied in a phase 3 trial (1042-0603, NCT01963208) and did not meet the primary efficacy endpoint in 2016, though efficacy and safety results are not available in published literature or clinicaltrials.gov.[13,14] The open-label extension was terminated.[13,14]

An open-label extension study is ongoing for long term efficacy data of ganaxolone in CDD. Efficacy and safety data are lacking in patients under 2 years of age. A study (NCT05249556) is planned for patients with CDD aged 6 months to 2 years for this important age group, given early age of onset of CDD.[15]

Clinical Safety:

Ganaxolone was generally well tolerated and there were no deaths and few discontinuations due to adverse events. Somnolence (ganaxolone 36% vs. placebo 16%) and pyrexia (ganaxolone 18% vs. placebo 8%) were the most common TEAE.[5] Somnolence and sedation are the most common adverse reactions resulting dose interruption and reduction of ganaxolone.[5] Use with other sedating agents (e.g. opioids, antidepressants, etc.) could increase side effects.[1] Use with certain cytochrome P450 inducers may decrease the serum concentration of ganaxolone and necessitate dosage adjustments, though the maximum dose should not be exceeded.[1]

There are no safety data available for people under 2 years of age. An open-label extension study beyond 17 weeks is ongoing. The most common adverse events noted in the drug labeling are detailed in **table 3**. This drug is controlled substance schedule V due to potential for abuse and dependence.

Table 3. Adverse Reactions[1]

Adverse Reaction	Ganaxolone (n=50)	Placebo (n=51)
Somnolence	38%	20%
Pyrexia	18%	8%
Upper respiratory tract infection	10%	6%
Sedation	6%	4%
Salivary Hypersecretion	6%	2%
Seasonal allergy	6%	0%
Bronchitis	4%	0%
Influenza	4%	2%
Gait disturbance	4%	2%
Nasal congestion	4%	2%

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduction in seizure frequency, duration, and/or severity

Primary Study Endpoint:

1) Percentage change in major motor seizure frequency

2) Improved quality of life
3) Reduction of global developmental impairment
4) Serious adverse events
5) Study withdrawal due to an adverse event

Table 4. Pharmacology and Pharmacokinetic Properties.[1]

Parameter	
Mechanism of Action	• Not fully known • Hypothesized as positive allosteric modulation of the gamma-aminobutyric acid type A ($GABA_A$) receptor in the central nervous system.
Oral Bioavailability	• Time to maximum plasma concentration (T_{max}) 2 to 3 hours. • High-fat meal increased maximum plasma concentration (C_{max}) 3-fold & area under the curve (AUC) 2-fold • Drug was administered with food during efficacy testing
Distribution and Protein Binding	99% protein bound
Elimination	55% fecal (2% unchanged) 18% renal (~0% unchanged)
Half-Life	34 hours
Metabolism	Metabolized via CYP3A4/5, CYP2B6, CYP2C19, and CYP2D6

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Knight et al.[4,5] DB, PC, Phase 3, MC, RCT	1. Ganaxolone (50 mg/mL) enterally TID 2. Placebo solution enterally TID Administered with food Titration over 4 weeks then 13 wk maintenance dosing -Max dose 63 mg/kg/day (pts ≤ 28 kg) or 1800 mg/day (pts >28 kg) -8 wk historical seizure period -6 wk prospective period to collect baseline date -17 wk DB treatment period -OL follow-up phase 1:1 randomization	<u>Demographics</u>: -Female: 79% -Median age: 6 years (range 3-11) -Median previous anti-Sz meds: 7 -Median current anti-Sz meds: 2 -White 92% -Asian 5% -Hispanic/Latino 9.9% -Concomitant Sz meds Valproate 33.7% Levetiracetam 25.7% Clobazam 24.8% Vigabatrin 21.8% -Baseline 28 d major motor sz frequency Median (IQR) 1. 54.0 (31.3-147.3) 2. 48.2 (18.7-120.0) -Seizure types Bilateral tonic 1. 71% 2. 76% Generalized tonic-clonic 1. 49% 2. 39% Atonic 1. 18% 2. 24% Bilateral clonic 1. 12% 2. 6% Focal to bilateral tonic-clonic 1. 14% 2. 12% <u>Key Inclusion Criteria</u>: -2 to 21 years -molecularly confirmed CDKL5 variant -hx of early-onset seizures uncontrolled despite trial of ≥2 antiseizure medications	<u>ITT</u>: 1. 50* 2. 51 <u>Attrition</u>: 1. 2 (4.0%) 2. 4 (7.8%)	<u>Primary Endpoint</u>: % change in major motor seizure frequency (28 day median value) from 6 week baseline assessment 1. -30.7% 2. -6.9 % Difference – 27.1% (95% CI, -47.9 to -9.6) p-value=0.0036 <u>Secondary Endpoints</u>: Proportion of patients with ≥ 50% reduction in major motor seizure frequency from baseline 1. 12/49 (24%) 2. 5/51 (10%) Difference 14.7% (95% CI, -4.7 to 33.8) p-value=0.064	NA NS	<u>Outcome</u> Death: 1. 0 2. 0 Serious TEAE: 1. 6 (12%) 2. 5 (10%) Any TEAE: 1. 43 (86%) 2. 45 (88%) Discontinuation due to TEAE: 1. 2 (4.0%)† 2. 4 (7.8%) Dose reduction or temporary discontinuation due to TEAE: 1. 11 (22%) 2. 8 (16%) Most frequent TEAE: Somnolence 1. 18 (36%) 2. 8 (16%) Pyrexia 1. 9 (18%) 2. 4 (8%) TRAE: 1. 35 (70%) 2. 22 (43%) Most frequent TRAE: Somnolence 1. 17 (34%) 2. 3 (6%)	NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (Low) Randomized centrally via interactive web response system. Baseline characteristics generally balanced, higher baseline median and IQR seizure frequency in ganaxolone group. <u>Performance Bias</u>: (Low) Identical taste and appearance of ganaxolone and placebo. <u>Detection Bias</u>: (Unclear) Staff, patients, caregivers, investigators, and sponsor masked to treatment randomization. Parent/caregiver maintained electronic daily seizure calendar. Parent/caregiver training for seizure identification and type not described. Possible unblinding secondary to side effects. <u>Attrition Bias</u>: (Low) Minimal and balanced attrition. Method for analyzing missing data not described. <u>Reporting Bias</u>: (Unclear) Phase 3 trial in different epilepsy population with negative outcomes unpublished.[13,14] <u>Other Bias:</u> (unclear) Sponsor contributed to study design, data collection, data analysis, data interpretation, data verification, and writing of the report. **Applicability**: <u>Patient</u>: Rare disease. Racial and ethnic makeup not reflective of Medicaid population. <u>Intervention</u>: Appropriate based on earlier phase testing. <u>Comparator</u>: Placebo. No standard comparator available. <u>Outcomes</u>: Appropriate. Longer term outcomes needed. <u>Setting</u>: 39 outpatient clinics (Australia, France, Israel, Italy, Poland, United Kingdom, United States [41.6%])

Author: Fletcher Date: Oct 2022

		-≥16 major motor sz per 28 d in each 4 wk period of 8 wk historic period before screening -up to 4 concomitant antiseizure medications with stable dosing for at least 1 mo before screening (exception: felbamate stable x6 mo) -Note: vagus nerve stimulation, ketogenic diet, modified Atkins diet do not count toward anti-sz medication limit but must be stable x3 mo before screening <u>Key Exclusion Criteria</u>: -West Syndrome -Sz of predominantly infantile spasm type -active CNS infx, demyelinating dz, degenerative neurologic dz, CNS dz deemed progressive via brain imaging -abnormal liver function -eGFR < 30 ml/min -use of adrenocorticotropic hormone or systemic corticosteroid -THC or CBD positive without Rx for EPIDIOLEX -moderate or strong inducers/inhibitors of cytochrome P450 3A4, 3A5, 3A7 *except* anti-sz medication (e.g. carbamazepine, phenytoin)				Seizure 1. 4 (8%) 2. 4 (8%)		

<u>Abbreviations</u>: ARR = absolute risk reduction; CBD = cannabidiol; CDKL5 = cyclin-dependent kinase-like 5 protein; CGI-I = Clinical Global Impression of Improvement; CI = confidence interval; CNS = central nervous system; d = days; DB = double-blind; dz = disease; eGFR = estimated glomerular filtration rate; hx = history; IQR = interquartile range; infx = infection; ITT = intention to treat; MC = multi-country; mITT = modified intention to treat; mo = month; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; OL = open-label; PC = placebo controlled; PP = per protocol; pts = patients; RCT = randomized controlled trial; Rx = prescription; sz = seizure; TEAE = treatment-emergent adverse event; THC = tetrahydrocannabinol; TID = three times daily; TRAE = treatment-related adverse event; wk = week

*one patient missing baseline seizure frequency and excluded from seizure frequency analysis

†one additional patient discontinued due to somnolence but remained in the study

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
carbamazepine	CARBAMAZEPINE	ORAL	ORAL SUSP	Y
carbamazepine	TEGRETOL	ORAL	ORAL SUSP	Y
carbamazepine	CARBAMAZEPINE	ORAL	TAB CHEW	Y
carbamazepine	CARBAMAZEPINE ER	ORAL	TAB ER 12H	Y
carbamazepine	TEGRETOL XR	ORAL	TAB ER 12H	Y
carbamazepine	CARBAMAZEPINE	ORAL	TABLET	Y
carbamazepine	EPITOL	ORAL	TABLET	Y
carbamazepine	TEGRETOL	ORAL	TABLET	Y
diazepam	DIASTAT	RECTAL	KIT	Y
diazepam	DIASTAT ACUDIAL	RECTAL	KIT	Y
diazepam	DIAZEPAM	RECTAL	KIT	Y
divalproex sodium	DEPAKOTE SPRINKLE	ORAL	CAP DR SPR	Y
divalproex sodium	DIVALPROEX SODIUM	ORAL	CAP DR SPR	Y
divalproex sodium	DEPAKOTE ER	ORAL	TAB ER 24H	Y
divalproex sodium	DIVALPROEX SODIUM ER	ORAL	TAB ER 24H	Y
divalproex sodium	DEPAKOTE	ORAL	TABLET DR	Y
divalproex sodium	DIVALPROEX SODIUM	ORAL	TABLET DR	Y
ethosuximide	ETHOSUXIMIDE	ORAL	CAPSULE	Y
ethosuximide	ZARONTIN	ORAL	CAPSULE	Y
ethosuximide	ETHOSUXIMIDE	ORAL	SOLUTION	Y
ethosuximide	ZARONTIN	ORAL	SOLUTION	Y
gabapentin	GABAPENTIN	ORAL	CAPSULE	Y
gabapentin	NEURONTIN	ORAL	CAPSULE	Y
gabapentin	GABAPENTIN	ORAL	TABLET	Y
gabapentin	NEURONTIN	ORAL	TABLET	Y
lacosamide	LACOSAMIDE	ORAL	TABLET	Y
lacosamide	VIMPAT	ORAL	TABLET	Y
lamotrigine	LAMICTAL	ORAL	TABLET	Y
lamotrigine	LAMOTRIGINE	ORAL	TABLET	Y
lamotrigine	SUBVENITE	ORAL	TABLET	Y
levetiracetam	KEPPRA	ORAL	SOLUTION	Y
levetiracetam	LEVETIRACETAM	ORAL	SOLUTION	Y
levetiracetam	KEPPRA	ORAL	TABLET	Y
levetiracetam	LEVETIRACETAM	ORAL	TABLET	Y
levetiracetam	ROWEEPRA	ORAL	TABLET	Y
methsuximide	CELONTIN	ORAL	CAPSULE	Y
oxcarbazepine	OXCARBAZEPINE	ORAL	ORAL SUSP	Y

oxcarbazepine	TRILEPTAL	ORAL	ORAL SUSP	Y
oxcarbazepine	OXCARBAZEPINE	ORAL	TABLET	Y
oxcarbazepine	TRILEPTAL	ORAL	TABLET	Y
phenobarbital	PHENOBARBITAL	ORAL	ELIXIR	Y
phenobarbital	PHENOBARBITAL	ORAL	TABLET	Y
phenytoin	DILANTIN-125	ORAL	ORAL SUSP	Y
phenytoin	PHENYTOIN	ORAL	ORAL SUSP	Y
phenytoin	DILANTIN	ORAL	TAB CHEW	Y
phenytoin	PHENYTOIN	ORAL	TAB CHEW	Y
phenytoin sodium extended	DILANTIN	ORAL	CAPSULE	Y
phenytoin sodium extended	PHENYTEK	ORAL	CAPSULE	Y
phenytoin sodium extended	PHENYTOIN SODIUM EXTENDED	ORAL	CAPSULE	Y
primidone	MYSOLINE	ORAL	TABLET	Y
primidone	PRIMIDONE	ORAL	TABLET	Y
rufinamide	BANZEL	ORAL	TABLET	Y
rufinamide	RUFINAMIDE	ORAL	TABLET	Y
tiagabine HCl	GABITRIL	ORAL	TABLET	Y
tiagabine HCl	TIAGABINE HCL	ORAL	TABLET	Y
topiramate	TOPAMAX	ORAL	TABLET	Y
topiramate	TOPIRAMATE	ORAL	TABLET	Y
valproic acid	VALPROIC ACID	ORAL	CAPSULE	Y
valproic acid (as sodium salt)	VALPROIC ACID	ORAL	SOLUTION	Y
zonisamide	ZONISAMIDE	ORAL	CAPSULE	Y
carbamazepine	EQUETRO	ORAL	CPMP 12HR	V
lamotrigine	LAMICTAL (BLUE)	ORAL	TAB DS PK	V
lamotrigine	LAMICTAL (GREEN)	ORAL	TAB DS PK	V
lamotrigine	LAMICTAL (ORANGE)	ORAL	TAB DS PK	V
lamotrigine	LAMOTRIGINE (BLUE)	ORAL	TAB DS PK	V
lamotrigine	LAMOTRIGINE (GREEN)	ORAL	TAB DS PK	V
lamotrigine	LAMOTRIGINE (ORANGE)	ORAL	TAB DS PK	V
lamotrigine	SUBVENITE (BLUE)	ORAL	TAB DS PK	V
lamotrigine	SUBVENITE (GREEN)	ORAL	TAB DS PK	V
lamotrigine	SUBVENITE (ORANGE)	ORAL	TAB DS PK	V
lamotrigine	LAMICTAL XR	ORAL	TAB ER 24	V
lamotrigine	LAMOTRIGINE ER	ORAL	TAB ER 24	V
lamotrigine	LAMICTAL ODT	ORAL	TAB RAPDIS	V
lamotrigine	LAMOTRIGINE ODT	ORAL	TAB RAPDIS	V
lamotrigine	LAMICTAL	ORAL	TB CHW DSP	V
lamotrigine	LAMOTRIGINE	ORAL	TB CHW DSP	V
lamotrigine	LAMICTAL XR (BLUE)	ORAL	TB ER DSPK	V

lamotrigine	LAMICTAL XR (GREEN)	ORAL	TB ER DSPK	V
lamotrigine	LAMICTAL XR (ORANGE)	ORAL	TB ER DSPK	V
lamotrigine	LAMICTAL ODT (BLUE)	ORAL	TB RD DSPK	V
lamotrigine	LAMICTAL ODT (GREEN)	ORAL	TB RD DSPK	V
lamotrigine	LAMICTAL ODT (ORANGE)	ORAL	TB RD DSPK	V
lamotrigine	LAMOTRIGINE ODT (BLUE)	ORAL	TB RD DSPK	V
lamotrigine	LAMOTRIGINE ODT (GREEN)	ORAL	TB RD DSPK	V
lamotrigine	LAMOTRIGINE ODT (ORANGE)	ORAL	TB RD DSPK	V
brivaracetam	BRIVIACT	ORAL	SOLUTION	N
brivaracetam	BRIVIACT	ORAL	TABLET	N
cannabidiol (CBD)	EPIDIOLEX	ORAL	SOLUTION	N
carbamazepine	CARBAMAZEPINE ER	ORAL	CPMP 12HR	N
carbamazepine	CARBATROL	ORAL	CPMP 12HR	N
cenobamate	XCOPRI	ORAL	TAB DS PK	N
cenobamate	XCOPRI	ORAL	TABLET	N
clobazam	SYMPAZAN	ORAL	FILM	N
clobazam	CLOBAZAM	ORAL	ORAL SUSP	N
clobazam	ONFI	ORAL	ORAL SUSP	N
clobazam	CLOBAZAM	ORAL	TABLET	N
clobazam	ONFI	ORAL	TABLET	N
diazepam	VALTOCO	NASAL	SPRAY	N
eslicarbazepine acetate	APTIOM	ORAL	TABLET	N
felbamate	FELBAMATE	ORAL	ORAL SUSP	N
felbamate	FELBATOL	ORAL	ORAL SUSP	N
felbamate	FELBAMATE	ORAL	TABLET	N
felbamate	FELBATOL	ORAL	TABLET	N
fenfluramine HCl	FINTEPLA	ORAL	SOLUTION	N
gabapentin	GABAPENTIN	ORAL	SOLUTION	N
gabapentin	NEURONTIN	ORAL	SOLUTION	N
gabapentin	GRALISE	ORAL	TAB ER 24H	N
gabapentin	GRALISE	ORAL	TAB24HDSPK	N
gabapentin enacarbil	HORIZANT	ORAL	TABLET ER	N
lacosamide	LACOSAMIDE	ORAL	SOLUTION	N
lacosamide	VIMPAT	ORAL	SOLUTION	N
lacosamide	VIMPAT	ORAL	TAB DS PK	N
levetiracetam	ELEPSIA XR	ORAL	TAB ER 24H	N
levetiracetam	KEPPRA XR	ORAL	TAB ER 24H	N
levetiracetam	LEVETIRACETAM ER	ORAL	TAB ER 24H	N
levetiracetam	SPRITAM	ORAL	TAB SUSP	N
midazolam	NAYZILAM	NASAL	SPRAY	N

oxcarbazepine	OXTELLAR XR	ORAL	TAB ER 24H	N
perampanel	FYCOMPA	ORAL	ORAL SUSP	N
perampanel	FYCOMPA	ORAL	TABLET	N
phenobarbital	PHENOBARBITAL	ORAL	ELIXIR	N
pregabalin	LYRICA	ORAL	CAPSULE	N
pregabalin	PREGABALIN	ORAL	CAPSULE	N
pregabalin	LYRICA	ORAL	SOLUTION	N
pregabalin	PREGABALIN	ORAL	SOLUTION	N
rufinamide	BANZEL	ORAL	ORAL SUSP	N
rufinamide	RUFINAMIDE	ORAL	ORAL SUSP	N
stiripentol	DIACOMIT	ORAL	CAPSULE	N
stiripentol	DIACOMIT	ORAL	POWD PACK	N
topiramate	TROKENDI XR	ORAL	CAP ER 24H	N
topiramate	QUDEXY XR	ORAL	CAP SPR 24	N
topiramate	TOPIRAMATE ER	ORAL	CAP SPR 24	N
topiramate	TOPAMAX	ORAL	CAP SPRINK	N
topiramate	TOPIRAMATE	ORAL	CAP SPRINK	N
topiramate	EPRONTIA	ORAL	SOLUTION	N
vigabatrin	SABRIL	ORAL	POWD PACK	N
vigabatrin	VIGABATRIN	ORAL	POWD PACK	N
vigabatrin	VIGADRONE	ORAL	POWD PACK	N
vigabatrin	SABRIL	ORAL	TABLET	N
vigabatrin	VIGABATRIN	ORAL	TABLET	N
gabapentin	NEURONTIN	ORAL	SOLUTION	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 31st, 2022

☐	1	Carbamazepine/tu [Therapeutic Use]	5227
☐	2	Diazepam/tu [Therapeutic Use]	4409
☐	3	divalproex.mp. or Valproic Acid/	13918
☐	4	Ethosuximide/tu [Therapeutic Use]	363
☐	5	Gabapentin/tu [Therapeutic Use]	345
☐	6	Lacosamide/tu [Therapeutic Use]	113
☐	7	Lamotrigine/tu [Therapeutic Use]	216
☐	8	Levetiracetam/tu [Therapeutic Use]	409
☐	9	methsuximide.mp.	103
☐	10	Oxcarbazepine/tu [Therapeutic Use]	66
☐	11	Phenobarbital/tu, th [Therapeutic Use, Therapy]	3449
☐	12	Phenytoin/tu [Therapeutic Use]	4397
☐	13	Primidone/tu [Therapeutic Use]	512
☐	14	rufinamide.mp.	325
☐	15	Tiagabine/tu [Therapeutic Use]	3
☐	16	Topiramate/tu [Therapeutic Use]	160
☐	17	Zonisamide/tu [Therapeutic Use]	54
☐	18	brivaracetam.mp.	384
☐	19	Cannabidiol/tu [Therapeutic Use]	740
☐	20	cenobamate.mp.	77
☐	21	Clobazam/tu [Therapeutic Use]	45
☐	22	eslicarbazepine.mp.	432
☐	23	Felbamate/tu [Therapeutic Use]	5
☐	24	Fenfluramine/tu [Therapeutic Use]	715

☐	25	Midazolam/tu [Therapeutic Use]	1609
☐	26	perampanel.mp.	751
☐	27	Pregabalin/tu [Therapeutic Use]	589
☐	28	rufinamide.mp.	325
☐	29	stiripentol.mp.	337
☐	30	Vigabatrin/tu [Therapeutic Use]	423
☐	31	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	34719
☐	32	limit 31 to yr="2021 -Current"	2021
☐	33	limit 32 to (adaptive clinical trial or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	350
☐	34	limit 33 to humans	344

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations August 12th, 2022

☐	# ▲	Searches	Results
☐	1	ganaxolone.mp.	156
☐	2	limit 1 to (english language and (clinical trial, all or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or "systematic review"))	20
☐	3	limit 2 to humans	12

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZTALMY® safely and effectively. See full prescribing information for ZTALMY.

ZTALMY® (ganaxolone) oral suspension, CXX [pending controlled substance scheduling]
Initial U.S. Approval: [pending controlled substance scheduling]

----------INDICATIONS AND USAGE----------

ZTALMY is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------

- Administer ZTALMY orally three times daily with food. (2.1)
- Titrate ZTALMY gradually according to the recommended schedules. See full prescribing information. (2.1)
- Dosage for patients weighing 28 kg or less (2.1):
  - the starting dosage is 6 mg/kg three times daily (18 mg/kg/day)
  - the maximum dosage is 21 mg/kg three times daily (63 mg/kg/daily).
- Dosage for patients weighing over 28 kg (2.1):
  - the starting dosage is 150 mg three times daily (450 mg daily)
  - the maximum dosage is 600 mg three times daily (1800 mg daily).

----------DOSAGE FORMS AND STRENGTHS----------

Oral suspension 50 mg/mL (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Somnolence and Sedation: Monitor for somnolence and sedation and advise patients not to drive or operate machinery until they have gained sufficient experience with ZTALMY. Concomitant use with other CNS depressants or alcohol could potentiate adverse effects. (5.1)
- Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts. (5.2)
- Withdrawal of Antiepileptic Drugs: ZTALMY should be withdrawn gradually to minimize the risk of increased seizure frequency and status epilepticus. (5.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence of at least 5% for ZTALMY and at least twice the rate of placebo) are somnolence, pyrexia, salivary hypersecretion, and seasonal allergy. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Marinus Pharmaceuticals, Inc. at 844-627-4687 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Cytochrome P450 inducers will decrease ganaxolone exposure. It is recommended to avoid concomitant use with strong or moderate CYP3A4 inducers; if unavoidable, consider a dosage increase of ZTALMY, but do not exceed the maximum recommended dosage. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2022

Appendix 4: Key Inclusion Criteria

Population	People with seizures or other conditions with crossover use of anti-epileptic therapy (e.g. neuropathy).
Intervention	Antiepileptic therapy
Comparator	vs. other antiepileptic therapy (for established medications in drug class) vs. placebo (for new agent ganaxolone)
Outcomes	Reduction in seizure frequency per month
Timing	Maintenance dosing
Setting	Outpatient

Cannabidiol

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Cannabidiol

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication AND is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?	**Yes:** Go to #5 Document current seizure frequency_____	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the prescribed dose greater than 25 mg/kg/day?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No**: Go to # 6
6. Are baseline liver function tests (LFTs) on file (serum transaminases and total bilirubin levels)? AND If LFTs are not within normal limits has the cannabidiol dose been adjusted per guidance for moderate to severe hepatic impairment in Table 1? LFTs should be obtained at 1 month, 3 months, and 6 months after starting treatment with cannabidiol and periodically thereafter as clinically indicated, after cannabidiol dose changes, or addition of other medications that are known to impact the liver.	**Yes:** Approve for 12 months Document results here: Date of lab work_____ AST_____ ALT_____ Total Bilirubin_____	**No**: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Are recent LFT's documented in patient records? AND If LFTs are not within normal limits has the cannabidiol dose been adjusted per guidance for moderate to severe hepatic impairment in Table 1?	**Yes:** Go to # 2 Document results here: Date of lab work_____ AST_____ ALT_____ Total Bilirubin_____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Go to #3 Document baseline and current seizure frequency_____	**No:** Pass to RPh. Deny for lack of treatment response.
3. Is the prescribed dose greater than 25mg/kg/day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 4
4. Is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Table 1: Dose Adjustments of Cannabidiol in Patients with Hepatic Impairment[1]

Hepatic Impairment	Starting Dosage	Maintenance Dosage Range in Patients with Lennox-Gastaut Syndrome (LGS) or Dravet Syndrome (DS)	Maintenance Dosage in Patients with Tuberous Sclerosis Complex (TSC)
Mild	2.5 mg/kg twice daily (5 mg/kg/day)	5 to 10 mg/kg twice daily (10 to 20 mg/kg/day)	12.5 mg/kg twice daily (25 mg/kg/day)
Moderate	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 to 5 mg/kg twice daily (5 to 10 mg/kg/day)	6.25 mg/kg twice daily (12.5 mg/kg/day)
Severe	0.5 mg/kg twice daily (1 mg/kg/day)	1 to 2 mg/kg twice daily (2 to 4 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)

1. Epidolex (cannabidiol) Oral Solution Prescribing Information. Carlsbad, CA; Greenwich Biosciences, Inc. July 2020.

P&T/DUR Review: 10/22 (SF); 10/21 (DM); 10/20; 6/20; 3/19; 1/19
Implementation: 11/1/20; 5/1/19; 3/1/19

Clobazam

Goal(s): To ensure appropriate drug use and restrict to indications supported by medical literature and funded by Oregon Health Plan.

Length of Authorization:
- 12 months

Requires PA:
Clobazam

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Does the patient have a diagnosis of Lennox-Gastaut syndrome and is the patient 2 years of age or older?	**Yes:** Go to #4	**No:** Go to # 5
4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have a diagnosis of Dravet Syndrome and is the patient 2 years of age or older?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has seizure frequency decreased since beginning therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for lack of treatment response.

Limitations of Use:

- Clobazam is not FDA-approved for epilepsy syndromes other than Lennox-Gastaut.
- National Institute for Health and Care Excellence (NICE) guidance recommends clobazam as a second line agent for management of Dravet Syndrome.[1]

1. National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management. nice.org.uk/guidance/cg137. Accessed July 30, 2018

P&T Review: *10/22 (SF); 10/21 (DM); 10/20; 6/20; 1/19; 3/18; 7/16; 3/15; 5/12*
Implementation: *3/1/19; 8/16, 8/12*

Fenfluramine

Goal(s):

Author: Fletcher Date: Oct 2022

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Fenfluramine

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have uncontrolled seizures on current baseline therapy with at least one other antiepileptic medication AND is fenfluramine intended to be prescribed as adjuvant antiepileptic therapy?	**Yes:** Go to #5 Document seizure frequency_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is the prescribed dose greater than 0.7 mg/kg/day or 26 mg/day OR 0.2 mg/kg/day or 17 mg/day in patients taking stiripentol plus clobazam?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No**: Go to # 6
6. Is baseline echocardiogram on file that was performed within past 6 months?	**Yes:** Approve for 12 months Document results here: Date of echocardiogram_____ Results_____	**No**: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has an echocardiogram been obtained within the past 6 months?	**Yes:** Go to # 2 Document results here: Date of echocardiogram____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Go to #3 Document baseline and current seizure frequency_____	**No:** Pass to RPh. Deny for lack of treatment response.
3. Is the prescribed dose greater than 0.7mg/kg/day or 26 mg/day or greater than 0.2 mg/kg/day or 17 mg/day in patients taking stiripentol plus clobazam?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 4

Renewal Criteria		
4. Is fenfluramine prescribed as adjuvant therapy and is patient adherent to all prescribed seizure medications?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *10/22 (SF); 10/21 (DM); 10/20*
Implementation: *11/1/20*

Ganaxolone Safety Edit

Goal:
- To ensure appropriate drug use and restrict to indications supported by medical literature

Length of Authorization:
- Up to 12 months

Requires PA:
- Ganaxolone

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the medication FDA-approved for the requested indication and patient age?	**Yes**: Go to #3	**No:** Go to #5

Approval Criteria		
3. What is the patient's current weight?	**Record weight:**_____ (within past 6 months) Go to #4	
4. Does the requested dosing align with the FDA-approved dosing?	**Yes:** Approve for up to 12 months	**No:** Go to #5
5. Has the patient already been taking this medication for longer than 4 weeks AND currently taking at time of this request?	**Yes:** Approve for 1 month and forward to medical director for review. (Abrupt withdrawal may precipitate increased seizures)	**No:** Pass to RPh. Deny; medical appropriateness.

P&T / DUR Review: *10/22 (SF)*
Implementation: *1/1/23*

Pregabalin

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

- Pregabalin and pregabalin extended release

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for pregabalin?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 2
2. What diagnosis is being treated?	Record ICD10 code	
3. Is the request for pregabalin immediate release?	**Yes:** Go to #4	**No:** Go to #5
4. Does the patient have a diagnosis of epilepsy?	**Yes:** Approve for lifetime	**No:** Go to #5
5. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; not funded by the OHP.
6. Has the patient tried and failed gabapentin therapy for 90 days or have contradictions or intolerance to gabapentin?	**Yes**: Approve for 90 days	**No:** Pass to RPh. Deny and recommend trial of gabapentin for 90 days

Renewal Criteria		
1. Does the patient have documented improvement from pregabalin?	**Yes**: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

Table 1. Pregabalin formulations for specific indications based on available evidence

Condition	Pregabalin	Pregabalin Extended-Release
Funded		
Diabetic Neuropathy	X	X

Postherpetic Neuropathy	X	X
Painful Polyneuropathy	X	
Spinal Cord Injury Pain	X	
Chemotherapy Induced Neuropathy	X	
Non-funded		
Fibromyalgia	X	

P&T Review: *10/22 (SF); 10/21 (DM); 10/20; 1/19; 7/18; 3/18; 3/17*
Implementation: *10/1/18; 8/15/18; 4/1/17*

Stiripentol

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature and funded by Oregon Health Plan.

Length of Authorization:

- Up to 12 months

Requires PA:

- Stiripentol capsules and powder for oral suspension

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for the FDA approved indication of Dravet syndrome in patients 6 months of age or older, weighing 7 kg or more, and taking clobazam?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is baseline white blood cell (WBC) and platelet counts on file within the past 3 months? <u>Note:</u> Labs should be assessed every six months while receiving stiripentol therapy.	**Yes:** Approve for 12 months Document results here: Date of lab work_____ WBC_____ Platelets_____	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Are recent WBC and platelet counts documented in patient records? <u>Note:</u> Labs should be assessed every six months while receiving stiripentol therapy.	**Yes:** Go to #2 Document results here: Date of lab work_____ WBC_____ Platelets_____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for lack of treatment response.

P&T/DUR Review: 10/22 (SF); 10/21 (DM); 10/20; 6/20; 1/19
Implementation: 3/1/2019

Author: Fletcher Date: Oct 2022

Topiramate

Goal(s):

- Approve topiramate only for funded diagnoses which are supported by the medical literature (e.g. epilepsy and migraine prophylaxis).

Length of Authorization:

- 90 days to lifetime

Requires PA:

- Non-preferred topiramate products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have diagnosis of epilepsy?	**Yes:** Approve for lifetime.	**No:** Go to #3
3. Does the patient have a diagnosis of migraine?	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime.	**No:** Go to #4
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Has the patient tried or are they contraindicated to at least two of the following drugs? • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic Document drugs tried or contraindications.	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of 2 covered alternatives.
6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?	**Yes:** Pass to RPh. Deny; not funded by the OHP AND weight loss drugs excluded by state plan.	**No:** Pass to RPh. Go to #7
7. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate. Use is unfunded: Deny; not funded by the OHP. If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: “Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal.”	

P&T Review: *10/22 (SF); 10/21 (DM); 10/20; 6/20; 5/19; 1/19; 7/18; 3/18; 3/17; 7/16; 3/15; 2/12; 9/07; 11/07*
Implementation: *4/18/15; 5/12, 1/12*