ganaxolone (Ztalmy®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO260

Description

Ganaxolone (Ztalmy) is an orally administered neuroactive steroid gamma-aminobutyric acid A ($GABA_A$) receptor positive modulator.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
ganaxolone (Ztalmy)	Seizures associated with CDKL5 Deficiency Disorder (CDD)	50 mg/mL oral suspension	≤ 28 kg: Monthly quantity (in mL) to allow for a maximum of 63 mg/kg per day
			> 28 kg: Monthly quantity (in mL) to allow for a maximum of 1800 mg (36 mL) per day

Initial Evaluation

I. **Ganaxolone (Ztalmy)** may be considered medically necessary when the following criteria are met:
   A. Member is two years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. Documentation of the member's weight, measured in the past three months (necessary for dose calculation); **AND**
   D. Will be used in combination with one or more antiseizure medications (e.g., clobazam [Onfi], valproate [Depakote], levetiracetam [Keppra], etc.); **AND**
   E. A diagnosis of **cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD)** as evidenced by all of the following:
      1. Documentation of pathogenic or likely pathogenic CDKL5 mutation; **AND**
      2. Provider attestation that seizure onset occurred by one year of age; **AND**
      3. Provider attestation that member has motor and cognitive delays; **AND**
      4. Documentation of baseline seizure frequency and severity**; AND**
      5. Seizures are refractory to three or more antiseizure medications (e.g., clobazam [Onfi], valproate [Depakote], lamotrigine [Lamictal], levetiracetam [Keppra],

rufinamide [Banzel], topiramate [Topamax], felbamate [Felbatol], stiripentol [Diacomit], zonisamide [Zonergan], vigabatrin [Sabril]).

II. Ganaxolone (Ztalmy) is considered investigational when used for all other conditions, including but not limited to:
   A. Infantile Spasms or West Syndrome
   B. Rett Syndrome
   C. Lennox-Gastaut Syndrome, Dravet Syndrome, Tuberous Sclerosis Complex
   D. Other non-FDA approved seizure disorders

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation of the member's weight that has been measured in the past three months (necessary for dose calculation); **AND**
IV. Ganaxolone (Ztalmy) will continue to be used in combination with one or more antiseizure medications; **AND**
V. Member has exhibited improvement or stability of seizure frequency or severity.

Supporting Evidence

I. Length of authorization for initial approval is six months as clinical benefits of ganaxolone (Ztalmy) were evaluated at 17 weeks in the pivotal trial. Six months is sufficient for assessment of treatment response and to initiate medication renewal request.
II. Ganaxolone (Ztalmy) is FDA-approved for use in patients two years of age and older. Safety and efficacy of ganaxolone (Ztalmy) in younger patients has not been evaluated. Other antiseizure medications have been evaluated for safety and efficacy in as early as infancy.
III. Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare genetic disorder caused by a mutation in the CDKL5 gene, which is responsible for normal brain development and function, that results in severe developmental delay, intellectual disability, and seizures. CDD presents as early as three months after birth, primarily in the form of frequent, refractory

spasms and seizures of various types. Additionally, motor and cognitive dysfunction become more prevalent over time, including behavioral dysregulation, movement disorders, hypotonia, visual impairment, sleep abnormalities, and gastrointestinal problems. CDKL5 gene mutations have also been identified in patients with infantile spasms, Rett, West and Lennox Gastaut Syndrome, autism and intractable epilepsy. However, CDD is a distinct disease characterized by symptoms of motor/cognitive delays and epilepsy with various seizure types within the first year of life. Given significant overlap with other types of developmental encephalopathies, treatment-resistant epilepsy, and movement disorders, diagnosis of CDD is made through presence of a pathogenic or likely pathogenic variant in the CDKL5 gene, presence of motor/cognitive delays, and onset of epilepsy within the first year of life.

IV. Given the specialized, high-touch care and monitoring required for CDD patients, ganaxolone (Ztalmy) must be prescribed by, or in consultation with, a neurologist.

V. There are no formal guidelines for management of CDD. Additionally, there are no currently available disease-modifying therapies for CDD, therefore treatment is supportive. Common treatment strategies for CDD-associated seizures include ketogenic diet, vagus nerve stimulator (VNS) placement, pharmacologic therapy with antiseizure medications, ACTH, or steroids, and neurosurgery. Experts recommend first-line therapy with a broad-spectrum antiseizure medication (e.g., valproate, levetiracetam, clobazam, zonisamide), and proceed with second trial or combination therapy as appropriate; VNS and neurosurgery are reserved for drug-resistant seizure. Seizure in CDD is known to be medically refractory, therefore it is common for CDD patients to have tried and continue to take multiple antiseizure medications concurrently. While ganaxolone (Ztalmy) is the only FDA-approved therapy for treatment of CDD-associated seizures, patients in the clinical program were required to be refractory to two or more antiseizure medications, the majority did not achieve clinically meaningful seizure reduction, and comparative efficacy to other antiseizure medications is unknown. Therefore, given the known extent of efficacy, established safety profile, and cost effectiveness of other antiseizure medications, at least three adequate efficacy trials are required prior to ganaxolone. Considering an abundance of available antiseizure medications, intolerance and early discontinuation do not meet definition of adequate efficacy trial.

VI. Ganaxolone (Ztalmy) was studied in one 17-week international, randomized, double-blind, placebo-controlled Phase 3 study: MARIGOLD. A total of 101 patients aged 2-21 years with molecularly confirmed CDD and a history of early-onset seizures uncontrolled by two or more antiseizure medications were enrolled. Use of up to four concomitant antiseizure medications during the study was allowed if stable on dose for at least one month, while patients being treated with glucocorticoids or ACTH were excluded. Population characteristics were as follows: 79% female, median age six years, median seven previous antiseizure medication trials, median two concomitant antiseizure medications including valproic acid, levetiracetam, clobazam and vigabatrin. The primary endpoint was percent change in median 28-day major motor seizure frequency (MMSF), with a 30.7% reduction in the ganaxolone group compared to a 6.9%

reduction in the placebo group (P=0.0036). Secondary endpoints included proportion of patients with ≥ 50% reduction in 28-day MMSF, otherwise known as clinically meaningful reduction in seizure frequency, and quality of life as assessed through the Clinical Global Impression of Improvement (CGI-I) score by clinician and caregiver, none of which were met. Most common adverse events were somnolence, pyrexia, and upper respiratory tract infection; ganaxolone (Ztalmy) is a controlled substance due to abuse and dependence potential and has a warning for somnolence/sedation. Overall, the benefit of ganaxolone (Ztalmy) is modest and potential confounding background therapy limits application and usefulness in the intended population.

VII. During clinical trials, participants received ganaxolone (Ztalmy) as an adjunct to antiseizure therapy, with the majority taking a median of two concomitant antiseizure medications. Background seizure medications included, but were not limited to, valproate, levetiracetam, clobazam, vigabatrin, clonazepam, topiramate, zonisamide, rufinamide, lamotrigine, oxcarbazepine, etc. Only one patient in the ganaxolone group was taking ganaxolone as monotherapy. As such, efficacy and safety of ganaxolone as monotherapy remain unknown.

Investigational or Not Medically Necessary Uses

I. Ganaxolone (Ztalmy) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Infantile Spasms or West Syndrome
   B. Rett Syndrome
   C. Lennox-Gastaut Syndrome, Dravet Syndrome, Tuberous Sclerosis Complex
   D. Other non-FDA approved seizure disorders

References

1. Ztalmy [Prescribing Information]. Marinus Pharmaceuticals, Inc: Radnor, PA. March 2022.
2. Knight EMP, Amin S, Bahi-Buisson N, et al. Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2022;21(5):417-427.
3. Olson HE, Demarest ST, Pestana-Knight EM, et al. Cyclin-dependent kinase-like 5 deficiency disorder: clinical review. Pediatr Neurol. 2019;97:18-25.
4. Olson HE, Daniels CI, Haviland I, et al. Current neurologic treatment and emerging therapies in CDKL5 deficiency disorder. J Neurodev Disord. 2021;13(1):40.
5. New drug review: Ztalmy (ganaxolone). IPD Analytics. April 2022. Accessed May 06, 2022.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
cannabidiol (Epidiolex®) Policy	Lennox-Gastaut Syndrome
	Dravet Syndrome
	Tuberous Sclerosis Complex
vigabatrin (Sabril®, Vigadrone®) Policy	West Syndrome (Infantile Spasms)
	Refractory complex partial epileptic seizure, adjunct therapy
stiripentol (Diacomit®) Policy	Dravet Syndrome
fenfluramine (Fintepla®) Policy	Dravet Syndrome

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2022