PRIOR AUTHORIZATION POLICY

POLICY: Antiseizure Medications – Ztalmy Prior Authorization Policy
- Ztalmy® (ganaxolone oral suspension – Marinus)

REVIEW DATE: 07/31/2024

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

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

Disease Overview

CDD is a rare, X-linked developmental epileptic encephalopathy caused by mutations in the CDKL5 gene.[2,3] This disorder can manifest in a broad range of clinical symptoms, including early-onset (< 3 months of age in 90% of patients [median of 5 weeks]), hypotonia, intractable epilepsy, and neurodevelopmental delay impacting cognitive, motor, speech, and visual function. Both cognitive impairment and refractory epilepsy in individuals with CDD are particularly severe; less than 50% of patients have reported a period of seizure freedom > 2 months, with only 12% of patients experiencing seizure freedom for > 12 months. The CDKL5 gene provides instructions for making proteins that are essential for normal brain and neuron development. The CDKL5 protein acts as a kinase, an enzyme that changes the activity of other proteins by adding a phosphate group at specific positions; however, it has not yet been determined which proteins are targeted by the CDKL5 protein. Many cases of CDD have been identified in boys, but because of the location of the

gene on the X chromosome, CDD primarily affects girls. Ztalmy is the first antiseizure medication that is FDA-approved for use in CDD and has been prospectively studied.

Clinical Efficacy

The efficacy of Ztalmy in patients with molecularly confirmed CDD was evaluated in one pivotal trial called the Marigold Study (n = 101).[4] Eligible patients were 2 to 21 years of age and had a molecularly confirmed CDKL5 variant that was considered pathogenic or likely to be pathogenic. Patients could remain on a regimen of up to four concomitant antiseizure medications during the trial, including (but not limited to) valproate, levetiracetam, clobazam, and vigabatrin. During the 17-week double-blind phase, the median 28-day major motor seizure frequency was 45.0 in the Ztalmy arm vs. 55.5 in the placebo arm. Compared with the 6-week baseline period, the median percentage change in 28-day major motor seizure frequency was statistically significantly improved (reduced) in the Ztalmy arm vs. the placebo arm (-30.7% vs. -6.9%, respectively; P = 0.0036).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ztalmy. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ztalmy as well as the monitoring required for adverse events and long-term efficacy, approval requires Ztalmy to be prescribed by or in consultation with a physician who specializes in the condition being treated.

- **Ztalmy® (ganaxolone oral suspension (Marinus)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indication

1. **Seizures Associated with Cyclin-Dependent Kinase-Like 5 (CDKL5) Deficiency Disorder.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥ 2 years of age; AND
   - **B)** Patient has a molecularly confirmed pathogenic or likely pathogenic mutation in the CDKL5 gene; AND
   - **C)** Patient has tried and/or is concomitantly receiving at least two other antiseizure medications; AND
     Note: This can include any two antiseizure medications, including but not limited to, clobazam, Epidiolex (cannabidiol oral solution), lacosamide, lamotrigine, levetiracetam, phenobarbital, rufinamide, topiramate, valproate, vigabatrin, zonisamide.
   - **D)** The medication is prescribed by or in consultation with a neurologist.

CONDITIONS NOT COVERED

Ztalmy® (ganaxolone oral suspension (Marinus)
is(are) considered experimental, investigational or unproven for ANY other use(s) including the following; criteria will be updated as new published data are available.

REFERENCES

1. Ztalmy® oral suspension [prescribing information]. Radnor, PA: Marinus; June 2023.
2. 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.
3. International Foundation for CDKL5 Research. About CDKL5. Available at: https://www.cdkl5.com/about-cdkl5/. Accessed on July 31, 2024.
4. 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;21:417-427.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	The policy name was changed from Antiepileptics – Ztalmy Prior Authorization Policy to Antiseizure Medications – Ztalmy Prior Authorization Policy. Throughout the criteria, reference to antiepileptic drugs was changed to antiseizure medications.	07/12/2023
Annual Revision	No criteria changes.	07/31/2024