VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

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

REVIEW DATE: 07/06/2022

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 antiepileptic drug 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 antiepileptic drugs during the trial. 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ztalmy is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Seizures Associated with Cyclin-Dependent Kinase-Like 5 (CDKL5) Deficiency Disorder.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   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) The medication is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ztalmy is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Ztalmy® oral suspension [prescribing information]. Radnor, PA: Marinus; March 2022.
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 5, 2022.
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
New Policy	--	07/06/2022