PHARMACY COVERAGE GUIDELINE

ZTALMY® (ganaxolone) oral

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require precertification is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

- **Criteria for initial therapy:** ZTALMY (ganaxolone) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist
  2. Individual is 2 years of age or older
  3. Individual has a confirmed diagnosis of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD)
  4. There is molecular confirmation of a pathogenic or likely pathogenic mutation in the *CDKL5* gene that is considered disease causing

5. Seizure onset occurred by 1 year of age

6. Seizures are inadequately controlled despite 2 or more antiseizure treatment regimens

7. Individual is on a stable regimen of multiple antiseizure medications

8. There are a minimum of 16 major motor seizures (i.e., bilateral tonic, generalized tonic-clonic, bilateral clonic, atonic, focal to bilateral tonic-clonic) per month during previous 2-month period

9. Documented failure (at least a 3-month trial), contraindication per FDA label, intolerance, or not a candidate for **TWO** previous treatment regimens that contain at least **TWO** of the following:
    a. Clobazam
    b. Felbamate
    c. Lamotrigine
    d. Levetiracetam
    e. Topiramate
    f. Valproate
    g. Vigabatrin
    h. Zonisamide

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** ZTALMY (ganaxolone) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met (**samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

2. Individual's condition has responded while on therapy with response defined as a 25% reduction in the frequency of major motor seizures (i.e., bilateral tonic, generalized tonic-clonic, bilateral clonic, atonic, focal to bilateral tonic-clonic) from baseline

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:
    a. Serious sedation, somnolence, lethargy, or hypersomnia that interferes with activities of daily living
    b. Emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior

5. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation

Renewal duration: 12 months

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- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

Description:

ZTALMY (ganaxolone) 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. Ganaxolone is an analog of the endogenous neurosteroid allopregnanolone, a derivative of progesterone.

The precise mechanism by which ganaxolone exerts its therapeutic effects in the treatment of seizures associated with CDD is unknown, but its anticonvulsant effects are thought to result from positive allosteric modulation of the gamma-aminobutyric acid type A (GABAA) receptor in the central nervous system.

CDD is a developmental encephalopathy caused by pathogenic variants in the *CDKL5* gene. This disorder includes early infantile onset refractory epilepsy, hypotonia, developmental intellectual and motor disabilities, and cortical visual impairment. The *CDKL5* gene provides instructions for making proteins that are essential for normal brain and neuron development. The CDKL5 protein has roles in cell proliferation, neuronal migration, axonal outgrowth, dendritic morphogenesis and synapse development and function in the brain. Some *CDKL5* gene mutations/variants are not disease-causing and are considered benign, therefore, to confirm a diagnosis the mutation must be considered disease-causing.

Seizure control is often difficult as no one anticonvulsant has been found to be uniformly effective, and often multiple anticonvulsants are needed. Median age of epilepsy onset is 6 weeks with 90% onset by 3 months. Eighty percent of children with CDD have daily seizures and 20% have weekly to monthly seizures. Information on the efficacy of seizure therapies is very limited. Medications with the highest rates in the reduction of seizure at 3 months include clobazam, felbamate, lamotrigine, steroids, valproic acid, vigabatrin, and zonisamide.

Definitions:

Common clinical characteristics and proposed minimal diagnostic criteria

Proposed minimal diagnostic criteria
• A pathogenic or likely pathogenic variant in the *CDKL5* gene • Motor and cognitive developmental delays • Epilepsy with onset in the first year of life
Common clinical characteristics

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- Epilepsy, early onset and refractory
- Severe global developmental delay
- Intellectual disability
- Hypotonia
- Cortical visual impairment
- Sleep disturbance
- Dyskinetic movements,
- Autonomic and breathing disturbances
- GI disturbances (reflux, constipation)
- Dysphagia

Resources:

Ztalmy (ganaxolone) product information, revised by Marinus Pharmaceuticals 06/2022. Available at http://ir.marinuspharma.com. Accessed June 30, 2022.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03572933: A Double-blind, Randomized, Placebo-controlled Trial of Adjunctive Ganaxolone Treatment in Children and Young Adults With Cyclin-dependent Kinase-like 5 (CDKL5) Deficiency Disorder (CDD) Followed by Long-term Open-label Treatment. Available from: http://clinicaltrials.gov. Last update posted November 13, 2020. Last verified November 2020. Accessed July 01, 2022.

Olson HE, Demarest ST, Pestana-Knight EM, et al.: Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder: clinical review. Pediatr Neurol. 2019 August; 97: 18–25. doi:10.1016/j.pediatrneurol.2019.02.015. Accessed July 01, 2022.