09-J4000-39

Original Effective Date: 01/01/23

Reviewed: 06/11/25

Revised: 07/15/25

Subject: Ganaxolone (Ztalmy) Oral Suspension

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare developmental disorder caused by CDKL5 gene mutations, which result in a nonfunctional CDKL5 protein (previously known as serine/threonine protein kinase 9 [STK9]). The CDKL5 gene is X-chromosome linked with mutations occurring four times more frequently in females than males. These mutations are estimated to occur in approximately 1 in 40,000 to 60,000 live births. CDD is classified as a developmental epileptic encephalopathy (DEE). Clinical presentation includes early-onset refractory epilepsy (i.e., 90% of patients within 3 months of birth), hypotonia, global developmental impairment, cortical visual impairment, and sleep difficulties. Therefore, multiple therapies (e.g., physical, occupational, speech) are utilized in addition to multiple anticonvulsant medications.

Ganaxolone (Ztalmy) is approved by the Food and Drug Administration (FDA) for the treatment of seizures associated with CDD in patients 2 years of age and older. Ganaxolone is a neuroactive steroid that acts as a positive allosteric modulator of gamma-aminobutyric acid (GABA) A receptors.

The safety and efficacy of ganaxolone was evaluated in one phase 3, double-blind, randomized, placebo-controlled study, which was conducted at 39 outpatient clinics in eight countries. Eligible patients included the following: 2-21 years of age, molecularly confirmed CDKL5 variant that was pathogenic or likely to be pathogenic, history of early-onset seizures uncontrolled after adequate trials of at least two anti-seizure medications, and at least 16 major motor seizures per 28 days in each of the 4-week periods of the 8-week historical seizure period at baseline. Concomitant anti-seizure medications were allowed but not to exceed four, and the anti-seizure medication dosing must be stable for 1 month before screening. Additionally, ketogenic diet, modified Atkins diet, and vagus nerve stimulation were allowed

but must have been consistent for 3 months prior to screening. Patients were excluded for various CNS disorders other than CDD, abnormal liver function, considerable renal impairment, and concomitant use of adrenocorticotropic hormone, glucocorticoids, and moderate or strong inhibitors or inducers of cytochrome P450 3A4, 3A5, and 3A7, with the exception of anti-seizure medications. There were 101 patients randomized 1:1 to ganaxolone (n=50) or placebo (n=51). Ganaxolone or placebo were administered three times per day and were titrated over 4 weeks to a maximum dose of 63 mg/kg per day (patients weighing less than or equal to 28 kg) or 1800 mg per day (patients weighing greater than 28 kg). Patients were then followed for 13 weeks of the maintenance period. The primary endpoint was the percentage change in major motor seizure frequency (expressed as a 28-day median value) from baseline to week 17. Secondary endpoints included reduction in major motor seizure frequency of at least 50% from baseline, percent of seizure-free days, and Clinical Global Impression of Improvement (CGI-I) scores. Eighty (79%) of the 101 patients were female, and the median age was 6 years (interquartile range: 3-10). Patients previously received a median of seven anti-seizure medications (interquartile range: 5-10) and were on a median of two concomitant anti-seizure medications (interquartile range: 1-3) during the study. The median 28-day major motor seizure frequency was 54 (interquartile range: 31.3-147.3) at baseline and 45 (interquartile range: 23.5-106.3) at week 17 for the ganaxolone group and 49.2 (interquartile range: 18.7-120) at baseline and 55.5 (interquartile range: 21.6-124.7) at week 17 in the placebo group. As compared to baseline, ganaxolone was associated with a -30.7% (interquartile range: -49.5 to -1.9) median change in 28-day major motor seizure frequency and placebo was associated with a -6.9% (interquartile range: -24.1 to 39.7) median change (p = 0.0036). The reduction in major motor seizure frequency of at least 50% from baseline was 12/49 (24%) for the ganaxolone group and 5/51 (10%) for the placebo group (p = 0.064). The median change in percentage of seizure-free days from baseline to week 17 was 4.9% (0 to 15.6) for the ganaxolone group and 0.2% (-3 to 15.2) for the placebo group. For the CGI-I caregiver-administered scale, 30/48 (63%) of patients in the ganaxolone group versus 21/48 patients (44%) in the placebo group were rated as minimally improved or better (OR 1.87; 95% CI: 0.89 to 3.91). For the CGI-I clinician-administered scale, 26/48 (54%) of patients in the ganaxolone group versus 20/48 (42%) of patients in the placebo group were rated as minimally improved or better (OR 1.41; 95% CI: 0.68 to 2.94). Treatment-emergent adverse events (AEs) were reported in 86% and 88% of patients in the ganaxolone and placebo groups, respectively, with serious AEs occurring in 12% of patients in the ganaxolone group and 10% of patients in the placebo group. Side effects most frequently associated with ganaxolone include somnolence, pyrexia, and upper respiratory tract infection. In general, ganaxolone may be a seizure treatment option for patients with genetically confirmed CDD with a high seizure burden who have an inadequate response to multiple anti-seizure medications.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of ganaxolone (Ztalmy) **meets the definition of medical necessity** when **ALL** of the following are met:

1. The member has a diagnosis of seizures associated with Cyclin-Dependent Kinase-Like 5 (CDKL5) Deficiency Disorder (CDD)
2. The member has an enzyme assay or genetic test demonstrating pathogenic or likely pathogenic mutation in the CDKL5 gene – Documentation must be submitted
3. The medication is prescribed by or in consultation with a neurologist
4. The dose does not exceed the following (a or b):
    a. Weight less than or equal to 28 kg: 63 mg/kg per day
    b. Weight greater than 28 kg: 1,800 mg per day

Approval duration: 6 months

Continuation of ganaxolone (Ztalmy) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 90 days before the authorization request must be submitted), **OR** the member has previously met all indication-specific initiation criteria.
2. The medication is prescribed by or in consultation with a neurologist
3. The medication dose does not exceed the following (a or b):
    a. Weight less than or equal to 28 kg: 63 mg/kg per day
    b. Weight greater than 28 kg: 1,800 mg per day

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- For the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older
- Dosage for patients weighing 28 kg or less:
    - starting dosage: 6 mg/kg three times daily (18 mg/kg/day)
    - maximum dosage: 21 mg/kg three times daily (63 mg/kg/daily)
- Dosage for patients weighing over 28 kg:
    - starting dosage: 150 mg three times daily (450 mg daily)

- maximum dosage: 600 mg three times daily (1800 mg daily)

- Administer ganaxolone orally three times daily with food.
- Titrate ganaxolone gradually according to the below recommended schedules, as outlined in the full prescribing information.

Titration for patients weighing 28 kg or less		
Dosage	**Total Daily Dosage**	**Days**
6 mg/kg three times daily	18 mg/kg/day	1 to 7
11 mg/kg three times daily	33 mg/kg/day	8 to 14
16 mg/kg three times daily	48 mg/kg/day	15 to 21
21 mg/kg three times daily	63 mg/kg/day	22 to ongoing

Titration for patients weighing over 28 kg			
Dosage	**mL per Dose**	**Total Daily Dosage**	**Days**
150 mg three times daily	3	450 mg	1 to 7
300 mg three times daily	6	900 mg	8 to 14
450 mg three times daily	9	1350 mg	15 to 21
600 mg three times daily	12	1800 mg	22 to ongoing

Dose Adjustments

- No dosage adjustment is necessary in patients with mild (Child-Pugh class A) or moderate (ChildPugh class B) hepatic impairment. However, dosage adjustments are recommended for patients with severe hepatic impairment (Child-Pugh class C).

Titration for patients with severe hepatic impairment and weighing 28 kg or less		
Dosage	Total Daily Dosage	Days
2 mg/kg three times daily	6 mg/kg/day	1 to 7
3.66 mg/kg three times daily	11 mg/kg/day	8 to 14
5.33 mg/kg three times daily	16 mg/kg/day	15 to 21
7 mg/kg three times daily	21 mg/kg/day	22 to ongoing

Titration for patients with severe hepatic impairment and weighing over 28 kg			
Dosage	mL per Dose	Total Daily Dosage	Days
50 mg three times daily	1	150 mg	1 to 7
100 mg three times daily	2	300 mg	8 to 14
150 mg three times daily	3	450 mg	15 to 21
200 mg three times daily	4	600 mg	22 to ongoing

- 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 ganaxolone, but do not exceed the maximum recommended dosage.

Drug Availability

- Oral suspension 50 mg/mL

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

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

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, not otherwise specified

ICD-10 Diagnosis Codes That Support Medical Necessity

G40.42	Cyclin-Dependent Kinase-Like 5 Deficiency Disorder

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if

based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

DEFINITIONS:

Cyclin-dependent kinase-like 5 deficiency disorder: rare, x-linked developmental and epileptic encephalopathy characterized by global developmental impairment and seizures that may begin in the first few months of life and are often treatment refractory.

RELATED GUIDELINES:

None applicable.

OTHER:

None applicable.

REFERENCES:

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2022. URL www.clinicalpharmacilogy-ip.com Accessed 05/26/25.
2. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 05/26/25.
3. 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.
4. Ztalmy (ganaxolone) [package insert]. Marinus Pharmaceutical. Radnor (PA): April 2024.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/11/25.

GUIDELINE UPDATE INFORMATION:

01/01/23	New Medical Coverage Guideline – Ganaxlone (Ztalmy) for seizures in genetically confirmed Cyclin-Dependent Kinase-Like 5 Deficiency Disorder.
08/15/23	Review and revision to guideline consisting of adding standard claims documentation language to the continuation criteria, inserting dosing for patients with severe hepatic impairment, and updating the references.
07/15/24	Review and revision to guideline consisting of updating the references.
07/15/25	Review and revision to guideline consisting of updating the references.