Original Effective Date: 12/08/2022
Current Effective Date: 06/13/2024
Last P&T Approval/Version: 04/24/2024
Next Review Due By: 04/2025
Policy Number: C24321-A

Ztalmy (ganaxolone)

PRODUCTS AFFECTED

Ztalmy (ganaxolone)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. SEIZURES ASSOCIATED WITH CYCLIN-DEPENDENT KINASE-LIKE 5 DEFICIENCY DISORDER:
1. Documented diagnosis of cyclin-dependent kinase-like 5 deficiency disorder
NOTE TO REVIEWER- diagnostic criteria can include:
(i) Genetically confirmed CDKL5 gene mutation, seizure onset by 1 year of age

(ii) Lack of independent ambulation by 2 years of age
(iii) Motor and cognitive developmental delays
AND

2. Documentation that seizures have been inadequately controlled by a trial of at least 2 antiepileptic drugs (e.g., clobazam, valproate, lamotrigine, levetiracetam, topiramate, felbamate, vigabatrin) or member has labeled contraindications to other antiepileptic drugs
AND
3. Documentation of baseline monthly seizure frequency [DOCUMENTATION REQUIRED]

CONTINUATION OF THERAPY:
A. SEIZURES ASSOCIATED WITH CYCLIN-DEPENDENT KINASE-LIKE 5 DEFICIENCY DISORDER:

1. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
AND
2. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms (e.g., reduced seizure activity, frequency, and/or duration)
AND
3. Documentation of continued medical need for the medication.

DURATION OF APPROVAL:
Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a neurologist, geneticist, or physician who specializes in the treatment of epileptic disorders. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests].

AGE RESTRICTIONS:
2 years of age and older

QUANTITY:
For patients weighing 28 kg or less: Maximum recommended dose is 63 mg/kg/day (1764 mg/day)
For patients weighing more than 28 kg: Maximum recommended dose is 1800 mg/day
Dosage should be increased based on tolerability no more frequently than every 7 days
See Appendix

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Anticonvulsants – Misc.

FDA-APPROVED USES:
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.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

Recommended titration schedule and maintenance dosage are based on body weight for patients weighing 28 kg or less. Dosage recommendations for patients weighing 28 kg or less and 28 kg or more are listed below:

Dosage for patients weighing 28 kg or less:

- Starting dosage is 6 mg/kg three times daily (18 mg/kg/day).
- Maximum dosage is 21 mg/kg three times daily (63 mg/kg/day).

Dosage for patients weighing more than 28 kg:

- Starting dosage is 150 mg three times daily (450 mg/day).
- Maximum dosage is 600 mg three times daily (1800 mg/day).

Dosage should be increased based on tolerability no more frequently than every 7 days. Titration increments should not exceed those shown above. Give all doses with food.

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 ZTALMY, but do not exceed the maximum recommended dosage.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare developmental disorder characterized by a cluster of clinical symptoms resulting from mutations in the CDKL5 gene. These mutations result in a nonfunctional CDKL5 protein (previously known as serine/threonine protein kinase 9 [STK9]). CDD has been classified as a developmental epileptic encephalopathy (DEE) because the genetic change causes epileptic activity and also severely hampers the development of affected individuals. Mutations of the X-linked CDKL5 gene are estimated to occur in approximately 1 in 40,000–60,000 live births, and the mutation is four times more prevalent in females compared to males. CDD follows a severe course in males, often leading to death in the first or second decade of life. CDD-associated epileptic spasms occur at the onset of the disease in 23% of patients and at various stages of the disease in 81% of patients.

Epilepsy usually beings in the first three months of life and includes tonic seizures, epileptic spasms without hypsarrhythmia, a seizure-free honeymoon period around one to two years old that may last up to 12 months, followed by multiple (2+) seizure types including sequences of mixed seizure type; cortical visual impairment associated with rotatory or horizontal nystagmus, dysconjugate gaze, and abnormal fixation; and global motor delays with hypotonia. Permanent regressions or progressive deterioration of neurological function is rare.

The clinical picture of CDD is often heterogeneous, and the primary symptoms include early-onset epilepsy (mostly drug refractory), poor muscle tone, sleep difficulties, bruxism, limited ability to walk, inability to speak (but may perform complex gestures/vocalization), limited hand skills, intellectual disability, and lack of eye contact (cortical vision disorders). In addition, a number of accompanying symptoms are sometimes reported, e.g., poor social interaction, gastrointestinal and orthopedic complaints, and dysmorphic facial features.

Most children with epilepsy achieve reasonably good seizure control with antiseizure drug therapy, but some are refractory despite numerous medications. Medical treatment failure is often apparent early in the course of treatment. Children who fail to respond to antiseizure drug monotherapy at adequate doses or do not tolerate effective doses should be started on a second antiseizure drug, although the likelihood of complete seizure remission decreases with each subsequent failed antiseizure drug trial. The first

antiseizure drug fails in 20 to 40 percent of children with epilepsy; lack of efficacy and side effects contribute roughly equally to treatment failure. Adding a second antiseizure drug is a reasonable next step when seizures are resistant to adequate doses of the initial drug.
ZTALMY is indicated for the treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder in patients 2 years of age and older.

MARIGOLD STUDY SUMMARY
A single, randomized, double-blind, placebo-controlled study was conducted in 50 patients between 2 and 19 years of age (Marigold trial/Study 1, NCT03572933) to establish the efficacy of Ztalmy for the treatment of CDD-associated seizures. Patients were randomized in a 1:1 ratio to receive either Ztalmy or placebo. Following a titration period of 21 days, patients in the Ztalmy arm weighing 28 kg or less received a maintenance dose of 21 mg/kg three times daily (with a maximum daily dose of 1800 mg), whereas patients in the Ztalmy arm weighing more than 28 kg received a maintenance dose of 600 mg three times daily. Out of the total 101 clinical trial participants, 96% of patients were taking 1–4 concomitant antiepileptic drugs (AEDs); the most frequently used AEDs (in at least 20% of patients) were valproate (42%), levetiracetam (32%), clobazam (29%), and vigabatrin (24%). The primary endpoint was a percentage change in the 28-day frequency of major motor seizures (defined similarly as in the 2-month period prior to screening) from a 6-week prospective baseline phase during the 17-week double-blind phase. Ztalmy demonstrated a median reduction of 30.7% in 28-day major motor seizure frequency compared with a median reduction of 6.9% in patients who received placebo. The most common adverse reactions (incidence of at least 5% for Ztalmy and at least twice the rate of placebo) are somnolence, pyrexia, salivary hypersecretion, and seasonal allergy.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Ztalmy (ganaxolone) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Ztalmy (ganaxolone) include: No labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:
Ztalmy must be administered with food. Ztalmy (ganaxolone) has been classified a schedule V controlled substance.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Ztalmy SUSP 50MG/ML (110ml bottle)

REFERENCES

1. Ztalmy [package insert]. Radnor, PA: Marinus Pharmaceuticals, Inc.; June 2023.
2. Sencen, L. (2022). CDKL5 Deficiency Disorder – NORD (National Organization for Rare Disorders). Retrieved 5 August 2022, from https://rarediseases.org/rare-diseases/cdkl5.
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4. Olson, H., Demarest, S., Pestana-Knight, E., Swanson, L., Iqbal, S., & Lal, D. et. al. (2019). Cyclin-Dependent Kinase-Like 5 Deficiency Disorder: Clinical Review. *Pediatric Neurology, 97, 18025.*
5. Dudley, R., Penney, S., & Buckley, D. (2009). First-Drug Treatment Failures in Children Newly Diagnosed With Epilepsy. *Pediatric Neurology, 40(2), 71-77.*
6. Jakimiec, M., Paprocka, J., & Śmigiel, R. (2020). CDKL5 Deficiency Disorder-A Complex Epileptic Encephalopathy. *Brain sciences*, *10*(2), 107. https://doi.org/10.3390/brainsci10020107.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information References	Q2 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Quantity References	Q2 2023
New Criteria	Q4 2022