ZTALMY (PREAUTHORIZATION REQUIRED)

X.205

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POLICY

Target Agents: Ztalmy

Ztalmy is 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.

Brand (generic)	GPI (NDC)	Multisource Code	Quantity Limit (per day or as listed)
Ztalmy (ganaxolone suspension)			
50mg/mL oral suspension	44604055002120	M, N, O, or Y	15mL per day

Initial Evaluation

I. Target Agent(s) may be considered **medically necessary** when ALL of the following are met:

A. Patient has diagnosis of cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) confirmed on genetic testing **AND**

B. Patient is 2 years of age or older **AND**

C. Patient not currently treated with adrenocorticotropic hormone (ACTh) or prednisone **AND**

II. ONE of the following:

A. The requested quantity (dose) does not exceed the program quantity limit **OR**

greater than the program quantity limit **AND**

2. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication **AND**

3. Information has been provided in support of therapy with a higher dose for the requested indication

Length of Approval: 12 months

Renewal Evaluation

I. Renewal of Target Agent(s) may be considered **medically necessary** when all of the following are met:

A. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND**

B. The patient has had clinical benefit with the requested agent **AND**

C. The patient does NOT have any FDA labeled contraindications to the requested agent **AND**

D. ONE of the following:

1. The requested quantity (dose) dose not exceed the program quantity limit **OR**

2. ALL of the following:

a. The requested quantity (dose) is greater than the program quantity limit **AND**

b. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication **AND**

requested indication

Length of Approval: 12 months

Dates

Original Effective
12-01-2022
Last Review
11-06-2024
Next Review
11-08-2025

CLINICAL RATIONALE

Cyclin-dependent kinase-like 5 (CDKL5) is a protein that has a crucial role in brain development and function, regulating neuronal proliferation, morphogenesis, and survival, as well as synaptic function, structure and plasticity. Pathogenic variants of CDKL5 lead to the development of CDKL5 deficiency disorder (CDD). CDD is a rare, X-linked disorder. CDD is a developmental and epileptic encephalopathy characterized by early-onset, refractory seizures and severe, global developmental impairment; cortical visual impairment, sleep disturbances, and hypotonia. CDD-associated seizures are usually refractory to antiseizure medications, and, when responsive to therapy, improvements are often short-lived (median duration of response of 6 months). Pathogenic CDKL5 variants can impair the excitatory-inhibitory neuronal balance due to alterations in glutamatergic and GABAergic mechanisms, including diminished GABAergic signaling.

Ganaxolone is a neuroactive steroid that acts as positive allosteric modulator of synaptic and extra-synaptic $GABA_A$ receptors to enhance GABAergic inhibitory tone. The effectiveness of ZTALMY for the treatment of seizures associated with CDD in patients 2 years of age and older was established in a single, double-blind, randomized, placebo-controlled study in patients 2 to 19 years of age (Study 1, NCT03572933; Marigold Study).

Patients enrolled in Study 1 (N=50 for ZTALMY; N=51 for placebo) had molecular confirmation of a pathogenic or likely pathogenic mutation in the CDKL5 gene, seizures inadequately controlled by at least 2 previous treatment regimens, and a minimum of 16 major motor seizures (i.e., bilateral tonic, generalized tonic-clonic, bilateral clonic, atonic, focal to bilateral tonic-clonic) per 28 days during a retrospective 2-month period prior to screening. Patients were allowed to be on a regimen of up to four concomitant

phase. Key exclusion criteria included: West syndrome or seizures of a predominantly infantile spasm type; active CNS infections, demyelinating disease, degenerative neurological disease or CNS disease deemed progressive via brain imaging; abnormal liver function; and considerable renal insufficiency. Concomitant use of adrenocorticotropic hormone, prednisone (or other glucocorticoids), or moderate or strong inducers or inhibitors of cytochrome P450 3A4, cytochrome P450 3A5, or cytochrome P450 3A7 was not allowed with the exception of antiseizure medications that are moderate or strong inducers or inhibitors of these enzymes (e.g., carbamazepine and phenytoin).

The primary efficacy endpoint was the 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. Patients treated with ZTALMY had a significantly greater reduction in the 28-day frequency of major motor seizures compared to patients receiving placebo (median reduction 30.7% vs 6.9%). Furthermore, antiseizure effects were observed during the 4-week titration period (median reduction from baseline 35.1% for ganaxolone vs 13.9% for placebo) and these effects persisted during the 13-week maintenance period (median reduction from baseline 29.4% vs 6.5%). The proportion of patients with a reduction in major motor seizure frequency from baseline of at lease 50% did not significantly differ between the ganaxolone and placebo groups.

Safety

Ztalmy has no contraindications or FDA Black Box Warnings

REFERENCES

2022

Ztalmy Prescribing Information. Marinus Pharmaceuticals, Inc. 06/2022

2022

Pestana Knight EM, Amin S, et al. Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomized, placebo-controlled phase 3 trial. Lancet Neurol. 2022 May; 21(5):417-427.

REVISIONS

on 11/8/2023 – no changes to policy.