ZTALMY®

The first FDA-approved treatment for seizures associated with CDD in patients 2 years of age and older

Ztalmy® (ganaxolone) oral suspension | 50 mg/mL

About ZTALMY® (ganaxolone)

ZTALMY is the first and only U.S. Food and Drug Administration-approved treatment specifically for seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients two years of age and older.[1,2]

ZTALMY Mechanism of Action

ZTALMY is a neuroactive steroid anticonvulsant that enhances GABAergic inhibitory effects beyond the synapse by modulating both synaptic and extra $GABA_A$ receptors.[2,3,4] The precise mechanism of action of how ZTALMY treats seizures in CDD is unknown.[2]

Phase 3 Marigold Trial

The Marigold study is a Phase 3 double-blind placebo-controlled trial in which patients were randomized and treated with ZTALMY or placebo. Participating patients suffered from approximately 16 or more major motor seizures per month that were not controlled by anti-seizure medications.

Pivotal population
Evaluated in a controlled study of 101 patients, aged 2 to 19 years, with refractory seizures associated with CDD[3]

Proven efficacy
Significantly reduced the frequency of monthly major motor seizures vs placebo over 17 weeks[3]

Demonstrated safety profile
Most common adverse reactions (incidence ≥5% and ≥2x placebo) were somnolence, pyrexia, salivary hypersecretion, and seasonal allergy[3]

About CDD

CDD is a serious and rare genetic disorder caused by a **mutation of the cyclin-dependent kinase-like 5 (*CDKL5*) gene**, which is located on the X chromosome and encodes proteins essential for normal brain function[5]

Diagnosed by **genetic testing** to determine if there is a mutation in the *CDKL5* gene[6]

Incidence is approximately **1:40,000 live births** and predominantly affects females[5]

Characterized by early-onset, **difficult-to-control seizures** and severe neurodevelopmental impairment[5]

Please see Important Safety Information on page 2

References

1 Marinus Pharmaceuticals. Marinus pharmaceuticals announces FDA approval of ZTALMY® (ganaxolone) for CDKL5 deficiency disorder [press release]. https://ir.marinuspharma.com/news/news-details/2022/Marinus-Pharmaceuticals-Announces-FDA-Approval-of-ZTALMY-ganaxolone-for-CDKL5-Deficiency-Disorder/default.aspx. Published March 18, 2022. Accessed April 2022.

2 ZTALMY® [package insert]. Radnor, PA: Marinus Pharmaceuticals. Inc.; 2022.

3 Pestana-Knight EM, 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. doi: https://doi.org/10.1016/S1474-4422(22)00077-1.

4 Martinez Botella G, Salituro FG, Harrison BL, et al. Neuroactive steroids. 1. Positive allosteric modulators of the (y-aminobutyric acid)a receptor: structure-activity relationships of heterocyclic substitution at C-21. J Med Chem. 2015;58(8):3500-3511.

5 Jakimiec M, Paprocka J, Śmigiel R. CDKL5 deficiency disorder—a complex epileptic encephalopathy. Brain Sci. 2020;10(2):107.

6 Demarest ST, Olson HE, Moss A, et al. CDKL5 deficiency disorder: relationship between genotype, epilepsy, cortical visual impairment, and development. Epilepsia. 2019;60(8):1733-1742.

INDICATION AND USAGE

ZTALMY is 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.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Somnolence and Sedation:** ZTALMY can cause somnolence and sedation. In a clinical study somnolence and sedation appeared early during treatment and were generally dose related. Other CNS depressants, including opioids, antidepressants, and alcohol, could potentiate these effects. Monitor patients for these effects and advise them not to drive or operate machinery until they have gained sufficient experience on ZTALMY to gauge whether it adversely affects their ability to drive or operate machinery.

- **Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs), including ZTALMY, increase the risk of suicidal thoughts or behavior. Monitor patients taking ZTALMY for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior. Advise patients, caregivers, and their families to be alert for these behavioral changes and report behaviors of concern immediately to healthcare providers. When considering ZTALMY, or any other AED, balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. If these symptoms emerge during treatment, consider whether it may be related to the AED or the underlying illness.

- **Withdrawal of Antiepileptic Drugs:** As with most AEDs, withdraw ZTALMY gradually to minimize the risk of increased seizure frequency and status epilepticus. If withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.

ADVERSE REACTIONS

The most common adverse reactions (incidence of at least 5% and at least twice the rate of placebo) were somnolence, pyrexia, salivary hypersecretion, and seasonal allergy.

DRUG INTERACTIONS

Cytochrome P450 inducers will decrease ganaxolone exposure. 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.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Use caution when ZTALMY is administered to pregnant women as there are no adequate data on the developmental risk associated with use in pregnant women. In animal studies, developmental adverse effects were observed following exposure during organogenesis or throughout gestation and lactation.

- **Lactation:** ZTALMY is excreted in human milk at concentrations resulting in a dose to the breastfed infant of less than 1% maternal dose. The effects of ZTALMY on milk production and the breastfed infant are unknown.

- **Hepatic Impairment:** Monitor patients with hepatic impairment for the incidence of adverse reactions. Patients with hepatic impairment may require a reduced dosage of ZTALMY.

DRUG ABUSE AND DEPENDENCE

ZTALMY contains ganaxolone, a Schedule V controlled substance (CV). Advise patients of the potential for abuse and dependence. It is recommended that ZTALMY be tapered according to the dosage recommendations unless symptoms warrant immediate discontinuation.

Please see the accompanying full **Prescribing Information**.

MARINUS

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