Ganaxolone (Ztalmy®) New Drug Update

April 2022

Nonproprietary Name	ganaxolone
Brand Name	Ztalmy
Manufacturer	Marinus
Form	Oral suspension (cherry-flavored)
Strength	50 mg/mL
FDA Approval	March 18, 2022
Market Availability	Anticipated July 2022; pending controlled substance scheduling
FDA Approval Classification	Orphan Drug, Priority Review, Rare Pediatric Disease
FDB Classification- Specific Therapeutic Class (HIC3)	To be determined

INDICATION[1]

Ganaxolone (Ztalmy) 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.

PHARMACOKINETICS

Following oral administration of ganaxolone, peak concentration is reached in 2 to 3 hours. Maximum concentration and area under the curve are increased when administered with a high-fat meal compared to fasted conditions. Ganaxolone is approximately 99% protein-bound and has a terminal half-life of 34 hours. Ganaxolone is metabolized by cytochrome p450 (CYP) 3A4/5, CYP2B6, CYP2C19, and CYP2D6 enzyme pathways. Following administration of a single radioactive-labeled dose, 55% of the dose was recovered in feces (2% unchanged) and 18% was recovered in urine.

CONTRAINDICATIONS/WARNINGS

Ganaxolone has no contraindications.

Ganaxolone can cause dose-related **somnolence and sedation**. Coadministration with other central nervous system (CNS) depressants (e.g., opioid, antidepressants) may potentiate these effects. Antiepileptic drugs have been associated with **suicidal behavior and ideation**. Due to the risk of increased seizure frequency and severity, ganaxolone should be **discontinued gradually**. Ganaxolone is a controlled substance and has **potential for abuse.**

DRUG INTERACTIONS

Ganaxolone serum concentration is reduced when coadministered with strong or moderate CYP450 inducers; avoidance is recommended. Increasing the ganaxolone dose (without exceeding the maximum recommended dose) may be considered when coadministration is unavoidable or when initiating or increasing the dose of an enzyme-inducing antiepileptic drug. Clinically significant pharmacokinetic alterations are not expected when ganaxolone is administered with CYP3A4 inhibitors or substrates.

COMMON ADVERSE EFFECTS

The most common adverse effects (incidence > 5%) reported with ganaxolone relative to placebo, respectively, in clinical trials, were somnolence (38% versus 20%), pyrexia (18% versus 8%), upper respiratory tract infection (10% versus 6%), sedation (6% versus 4%), salivary hypersecretion (6% versus 2%), and seasonal allergy (6% versus 0%).

SPECIAL POPULATIONS

Pregnancy

Based on data from animal studies and mechanism of action, ganaxolone may cause embryofetal harm when administered to a pregnant patient. Patients who are taking ganaxolone during pregnancy are encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry which monitors pregnancy outcomes in patients exposed to antiepileptic drugs during pregnancy.

Pediatrics

Safety and efficacy of ganaxolone have not been established in pediatric patients < 2 years of age.

Geriatrics

Clinical trials did not include patients ≥ 65 years of age to inform of differences in pharmacokinetics or safety of ganaxolone compared to younger patients.

Hepatic Impairment

Exposure to ganaxolone may be increased in patients with hepatic impairment. Close monitoring and consideration of dose reduction is recommended.

Renal Impairment

As renal excretion of ganaxolone is minimal, renal impairment is unlikely to affect drug exposure.

DOSAGES

Ganaxolone is administered 3 times a day with food. Recommended dose and titration schedule are dependent on weight. Dose increases should be made based on tolerability, occurring no more frequently than every 7 days.

Recommended Titration Schedule

Days of Therapy	Dosage	Total Daily Dose
Patients weighing ≤ 28 kg		
1 to 7	6 mg/kg 3 times daily	18 mg/kg/day
8 to 14	11 mg/kg 3 times daily	33 mg/kg/day
15 to 21	16 mg/kg 3 times daily	48 mg/kg/day
22 and ongoing	21 mg/kg 3 times daily	63 mg/kg/day
Patients weighing > 28 kg		
1 to 7	150 mg 3 times daily	450 mg
8 to 14	300 mg 3 times daily	900 mg
15 to 21	450 mg 3 times daily	1,350 mg
22 and ongoing	600 mg 3 times daily	1,800 mg

Unused suspension should be discarded 30 days after first opening the bottle.

CLINICAL TRIALS[2,3]

A literature search was performed using "ganaxolone" and "seizure."

Marigold study (NCT03572933): the safety and effectiveness of ganaxolone in patients with CDD-associated seizures were assessed in this phase 3 study. The randomized, double-blind, placebo-controlled trial enrolled 101 patients 2 to 19 years of age with a confirmed pathogenic or likely pathogenic mutation in the *CDKL5* gene. Participants were required to have experienced a minimum of 16 major motor seizures per 28 days during a 2-month period prior to screening and inadequate seizure control with at least 2 previous treatment regimens. Patients experiencing predominantly infantile spasms were excluded. Enrolled patients were maintained on a stable regimen of ≤ 4 anti-seizure medications. Concomitant antiepileptic drugs were being used by 96% of participants. Patients were randomized in a 1:1 ratio to receive placebo or a weight-based dose of ganoxolone with a 21-day titration period. Patient weighing ≤ 28 kg were titrated to a maximum dose of 63 mg/kg/day and those weighing > 28 kg were titrated to a maximum dose of 1,800 mg/day. The primary endpoint was change in the 28-day frequency of major motor seizures after 17 weeks on a maintenance dose of ganaxolone. Median seizure frequency per 28 days at baseline was 54 seizures in the treatment group and 49 seizures in the placebo group. Hence the median percent change in seizure frequency from baseline was reduced by 31% in the ganaxolone group versus 7% with placebo (p=0.0036). More than 10% of patients experienced a reduction in seizure frequency of ≥ 50% to < 75% with ganoxolone treatment, while > 20% of patients in the ganaxolone group saw no reduction in seizure frequency. Twenty-two percent of patients in the ganaxolone arm required a dose interruption or reduction secondary to adverse reactions compared to 16% of patients in the placebo arm.

OTHER DRUGS USED FOR CONDITION[4,5]

Ganaxolone is the first and only anticonvulsant medication indicated for seizures associated with CDD. Other anticonvulsant drugs are used off-label in practice. Some patients with CDD have experienced seizure improvement with vagal nerve stimulation or adhering to a ketogenic diet.

PLACE IN THERAPY[6,7,8,9,10]

CDKL5 deficiency disorder (CDD) is a developmental epileptic encephalopathy (DEE) resulting from *de novo* (non-hereditary) mutations of the X-linked *CDKL5* gene. The incidence of CDD is estimated to be between 1 in 40,000 to 60,000 live births and is 4 times more prevalent in females; however, disease severity may be greater in males. The disorder is characterized by seizures, with onset typically in the first 3 months of life, and significant developmental impairments affecting cognitive, motor, speech, and visual function. Other common symptoms include poor muscle tone, gastroesophageal reflux, constipation, respiratory infections, and sleep disturbances. More than 30 different types of seizures have been reported in patients with CDD. Daily seizures occur in approximately 80% of children with CDD. They are typically severe and refractory to anticonvulsant medications.

The American Academy of Neurology (AAN) guidelines for treatment-resistant (TR) epilepsy and infantile spasms do not specifically address epilepsy related to CDD and have not been updated since the approval of ganaxolone (Ztalmy); however, they make recommendations for managing adult and pediatric patients with TR epilepsy. For TR generalized epilepsy, topiramate, lamotrigine, and levetiracetam are recommended as adjunctive therapy. For pediatric patients with TR focal epilepsy, the guidelines endorse the use of gabapentin, lamotrigine, oxcarbazepine, and topiramate as "effective" adjunctive therapy, and levetiracetam and zonisamide as "probably effective." The AAN recommends adrenocorticotropic hormone (ACTH) or vigabatrin for infantile spasms.

Ganaxolone is the first and only anticonvulsant medication specifically indicated for seizures associated with CDD. Other anticonvulsant drugs are used off-label with variable efficacy, and often multiple agents are needed to achieve control. In the phase 3 Marigold trial, anticonvulsants most frequently used by study participants were valproate, levetiracetam, clobazam, and vigabatrin. A descriptive study reviewed the current treatment of 168 CDD patients receiving care at Centers of Excellence and/or registered in the NIH-funded Natural History Study (NHS) of Rett and Related Disorders. Of the 33 different anticonvulsants prescribed, the most frequently utilized were levetiracetam, topiramate, clobazam, and phenobarbital. Aside from anticonvulsant medications, some patients were using non-FDA-approved cannabis derivatives, ACTH, and oral corticosteroids. A review of anticonvulsants in 39 patients with CDD found significant inter-individual variability in response. Responder rate to at least 1 anticonvulsant medication was 69% at 3 months and declined to 24% at 12 months.

Market availability of ganaxolone is expected following controlled substance scheduling by the Drug Enforcement Agency (DEA).

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Anticonvulsants
Clinical Edit	**Initial Approval Criteria** ▪ Patient is ≥ 2 years of age; **AND** ▪ Patient has a diagnosis of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) confirmed with genetic testing; **AND** ▪ Patient has tried ≥ 2 other anticonvulsant medications; **AND** ▪ Patient will avoid concomitant therapy with moderate or strong CYP450 inducers (e.g., carbamazepine, phenobarbital, phenytoin, omeprazole), or if concomitant therapy is unavoidable, dose adjustments will be considered; **AND** ▪ Ganaxolone is prescribed by or in consultation with a neurologist. **Renewal Criteria** ▪ Patient must continue to meet the above criteria; **AND** ▪ Prescriber attests to stabilization of disease or reduction in seizure frequency from baseline; **AND** ▪ Patient has not experienced any treatment-restricting adverse effects (e.g., somnolence, pyrexia, suicidal thoughts or behavior)
Quantity Limit	1,080 mL per 30 days Maximum daily dose = 1,800 mg
Duration of Approval	Initial: 6 months Renewal: 1 year
Drug to Disease Hard Edit	None

REFERENCES

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2 Ztalmy [package insert]. Radnor, PA; Marinus; March 2022.
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