New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Ztalmy® (ganaxolone) [Marinus Pharmaceuticals, Inc.] (zuh tal' mee)**
Dosage Formulations:	50 mg/mL cherry flavored oral suspension in a 110 mL bottle Packaged in cartons of 1 bottle or 5 bottles
FDA Approval Date: **FDB File Date:**	FDA: March 18, 2022 FDB: June 19, 2022
Indication:	Treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older
Mechanism of Action:	The precise mechanism by which ganaxolone exerts its therapeutic effects in the treatment of seizures associated with CDD is unknown, but its anticonvulsant effects are thought to result from positive allosteric modulation of the gamma-aminobutyric acid type A ($GABA_A$) receptor in the central nervous system (CNS).
Dose/ Administration:	• Ztalmy is administered by mouth three times daily with food. • The recommended titration schedule and maintenance dosage are based on body weight for patients weighing 28 kg or less. Dosage should be increased based on tolerability no more frequently than every 7 days and titration increments should not exceed those listed below.

Ztalmy Recommended Titration Schedule for Patients Weighing ≤ 28 kg		
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

Ztalmy Recommended Titration Schedule for Patients Weighing > 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	1,350 mg	15 to 21
600 mg three times daily	12	1,800 mg*	22 to ongoing

* Maximum recommended dose

- If the need to discontinue Ztalmy arises, the dose should be gradually decreased. As with all antiepileptic drugs, abrupt discontinuation should be avoided, when possible, 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.

<u>Administration/Storage</u>

- Shake the bottle thoroughly for at least one minute and then wait one minute before measuring and administering each dose.
- Administer each dose with food.
  - Ztalmy was administered with food in the clinical study; the efficacy when administered in the fasted state is unknown. When administered with a high-fat meal, the C_{max} and AUC increased by 3- and 2-fold, respectively when compared to administration under fasted conditions.
- Store in an upright position at room temperature (59°F to 86°F).
- Any used product should be discarded after 30 days of first opening the bottle or the "Discard After" date on the bottle, whichever is sooner.

Disease State Clinical Highlights:	• Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD), first discovered in 2004, is a rare developmental disorder caused by pathogenic variants in the *CDKL5* gene resulting in a nonfunctional CDKL5 protein. The CDKL5 protein is involved in the proliferation, neuronal migration and formation, neuronal growth, and development and functioning of synapses during brain maturation. • More than 265 pathogenic variants within the X-linked *CDKL5* gene have been reported. The variants are estimated to occur in approximately 1 in 40,000-60,000 live births and are four times more prevalent in females compared to males. In males, the condition tends to be more severe, often leading to death in the first or second decade of life. Most *CDKL5* gene pathogenic variants are "de novo" in that they occur spontaneously and are not passed down through families. • CDD is a form of developmental epileptic encephalopathy (DEE) that is characterized by early-onset (often treatment-refractory) epilepsy, generalized hypotonia, psychomotor developmental disorders, cortical vision disorders, and significant intellectual disability. Additional symptoms may include poor social interactions, poor eye contact, hand stereotypy, vegetative disorders, gastrointestinal (i.e., constipation, gastroesophageal reflux disease) and orthopedic (i.e., scoliosis) complaints, feeding and swallowing disorders, or dysmorphic facial features. • The first episodes of epileptic seizures occur in the first six weeks of life for 96% of patients and within the first three months in 90% of patients. Types of epileptic episodes vary and may include epileptic spasms, absence, partial, myoclonic, tonic seizures, or limb spasms. The seizures become generalized or multifocal over time; tonic-clonic manifestations being the most prevalent. • Brain MRI studies rarely show any abnormalities in the first months of life. Most patients present with changes in neuroimaging by age 6, however the changes are not specific and cannot be used as a basis for diagnosis, differentiation, or prognosis. • No clinical guidelines currently exist to guide the management of CDD.
Drug Clinical Highlights:	• Ztalmy is the first FDA-approved CDD-specific therapy. • The FDA reviewed Ztalmy under Priority Review and granted the product Orphan Drug and Rare Pediatric Disease designations. With the approval, Marinus was awarded a Pediatric Disease Priority Review Voucher. • Schedule V controlled substance. Ganaxolone is a new molecular entity and although there is no evidence regarding its diversion, illicit manufacturing, or deliberate ingestion, it does have sedative effects and is likely to have abuse potential. • Contraindications: none • Warnings and Precautions: ○ Somnolence and sedation: patients should not drive or operate machinery until they have gained sufficient experience with Ztalmy. Concomitant use of other CNS depressants or alcohol could potentiate adverse effects. ○ Suicidal behavior and ideation: monitor patients for suicidal thoughts and behavior. ○ Withdrawal of antiepileptic drugs: Ztalmy should be withdrawn gradually to minimize the risk of increased seizure frequency and status epilepticus. • Adverse Reactions (≥ 5% and greater than placebo): somnolence (38%), pyrexia (18%), upper respiratory tract infection (10%), sedation (6%), salivary hypersecretion (6%), seasonal allergy (6%). ○ In clinical trials, the adverse reactions leading to discontinuation in Ztalmy-treated patients were somnolence (1 patient) and seizure (1 patient). Of the patients treated with Ztalmy, 22% had dosing interrupted or reduced because of any adverse reaction, compared to 16% of placebo-treated patients. The most frequent adverse reactions leading to a dose interruption or reduction in Ztalmy-treated patients were somnolence (10%) and sedation (2%). • Drug Interactions: ○ Strong or moderate cytochrome P450 inducers: concomitant use with strong or moderate CYP3A4 inducers should be avoided as they will decrease Ztalmy

exposure. If unavoidable, consider a dosage increase of Ztalmy, but do not exceed the maximum recommended dosage.
    - Concomitant use with CNS depressants and alcohol: concomitant use may increase the risk of somnolence and sedation.
- Use in Special Populations:
    - Pregnancy: there is no available data on the use of Ztalmy in pregnant women. In animal studies, adverse effects on development were observed in mice (fetal malformations) and rats (neurobehavioral and growth impairment) following exposure during organogenesis (mouse) or throughout gestation and lactation (rat) at maternal exposures lower than that in human adults at the maximum recommended human dose of 1,800 mg. In addition, neuronal death was observed in rats exposed to Ztalmy during a period of brain development that begins during the third trimester of pregnancy in humans and continues during the first few years after birth. Women taking Ztalmy should be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry if they become pregnant.
    - Lactation: Ztalmy is excreted in human milk; the effects of Ztalmy on milk production and the breastfed infant are unknown.
    - Hepatic impairment: Ztalmy undergoes clearance via the hepatic route; hepatic impairment can increase Ztalmy exposure.
    - Renal impairment: renal excretion is a minor pathway in the elimination of Ztalmy therefore, renal impairment is unlikely to result in clinically significant increases in Ztalmy exposure.
- Clinical Studies
    - MARIGOLD trial/Study 1 (n=101) (NCT03572933): Efficacy of Ztalmy for the treatment of CDD-associated seizures was established in a randomized, double-blind, placebo-controlled study in patients aged 2 to 19 years.
    - Inclusion Criteria:
        - Genetically confirmed *CDKL5* gene pathogenic variants, seizure onset by 1 year of age, and lack of independent ambulation by 2 years of age
        - Failure to control seizures despite two or more antiseizure medications
        - At least 16 major motor seizures (bilateral tonic, generalized tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic) every 28 days during retrospective 2-month period prior to screening
        - On a stable regimen of 0 to 4 antiepileptic medications (vagus nerve stimulator, ketogenic diet, and modified Atkins diet did not count toward this limit)
    - Exclusion Criteria:
        - Previous exposure to ganaxolone
        - West syndrome with hypsarrhythmia pattern on EEG or seizures predominantly of infantile spasms type
        - Use of adrenocorticotropic hormone (ACTH), prednisone or other glucocorticoid or use of moderate or strong inducers or inhibitors of CYP3A4/5/7
        - Use of tetrahydrocannabinol (THC) or cannabidiol (CBD) was prohibited during the double-blind phase, unless the patient had a prescription for Epidiolex®
    - Baseline Characteristics:
        - 96% of patients were taking between 1 to 4 concomitant antiepileptic drugs. The most frequently used (in at least 20% of patients) were valproate (42%), levetiracetam (32%), clobazam (29%), and vigabatrin (24%).
        - Approximately 78% of patients were female, 92% were White, and mean age was 6.8 years (range 2 to 19).
    - Treatment Regimen:
        - Following a 21-day titration period, patients in the Ztalmy arm weighing ≤ 28 kg received a maintenance dosage of 21 mg/kg three times daily (with a maximum daily dose of 1,800 mg)
        - Patients in the Ztalmy arm weighing > 28 kg received a maintenance dosage of 600 mg three times daily

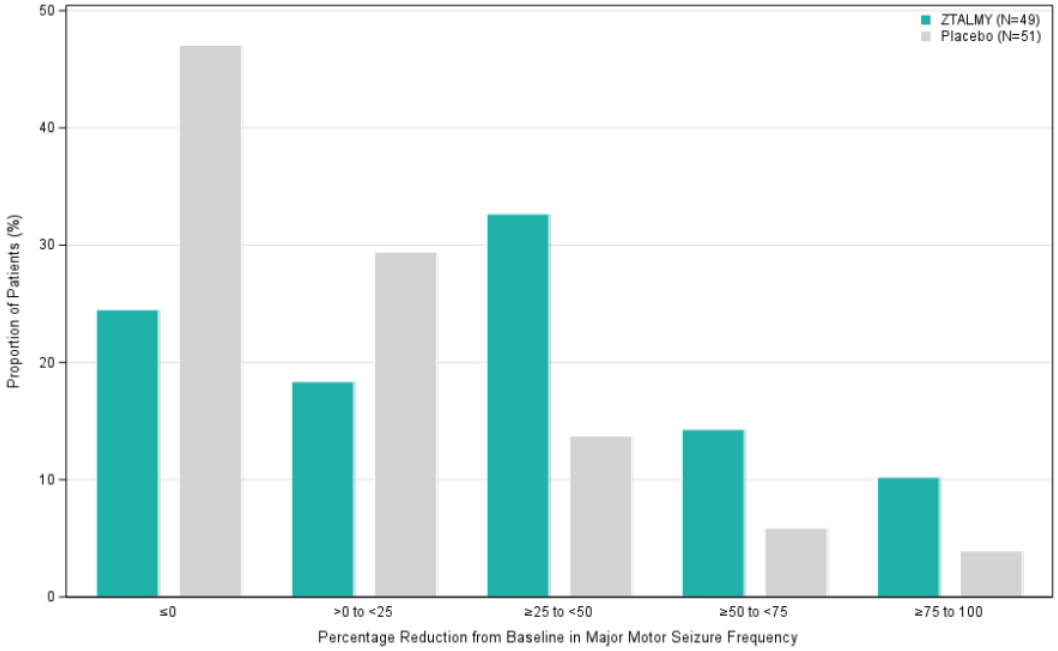
- Primary Endpoint: percentage change in the 28-day frequency of major motor seizures (defined similarly as the 2-month period prior to screening) relative to the 6-week prospective baseline phase during the 17-week double-blind phase

- Efficacy Results:

Change in Frequency of Major Motor Seizures per 28 Days in Patients with CDD		
Frequency of Major Motor Seizures	**Ztalmy (N=49)**	**Placebo (N=51)**
Prospective baseline phase median seizure frequency	54	49
Median percent change from baseline during treatment	-31	-7
P value compared to placebo*	0.0036	-

*Obtained from a Wilcoxon rank-sum test

Proportion of Patients by Category of Seizure Response for ZTALMY and Placebo in Patients with CDD



- Patients in the study who participated in an open-label extension phase for at least 12 months experienced a median 49.6% reduction in motor seizure frequency.

Price Per Unit (WAC):

- $2,425 per 110 mL bottle
- Cost per patient is variable based on weight
- Estimated annual cost for 17 kg patient: $174,600

Therapeutic Alternatives:

- No targeted therapy exists for the treatment of CDD; management is symptom-based. In addition to antiseizure medications, patients should be provided with multidisciplinary care, including physiotherapy, occupational therapy, neurological speech therapy, and dietetics. Choice of antiepileptic therapy is based on current seizure type and electroencephalogram recordings however, 84% of patients develop resistance to antiepileptics.
- Primary goals of therapy are to control the most problematic complaints that increase disability, increase possibility for patient development, and improve quality of life for both the patient and family.
- Non-pharmacologic options: physical therapy, occupational therapy, and speech and augmentative communication therapy, ketogenic diet, vagus nerve stimulation, callosotomy.

- Patients with *CDKL5* pathogenic variants constitute the group with lowest effectiveness of ketogenic diet treatment among other genetic epileptic encephalopathies.

- Pharmacologic Options: no single antiepileptic has been found to be uniformly effective, and often multiple antiepileptics are needed.
  - An open-label, compassionate use study evaluated therapy with cannabidiol in patients with CDD, Aicardi, Doose, and Dup15q syndromes. Patients enrolled were aged 1-30 years, had a diagnosis of severe childhood-onset epilepsy (CDD, n=20; Aicardi syndrome, n=19; Dup15q syndrome, n=8), and had received cannabidiol for ≥ 10 weeks. Patients with CDD had a history of 3-6 baseline background antiepileptics. Therapy with cannabidiol resulted in a reduction of median convulsive seizure frequency from baseline (n=17) by 40.8% by week 12 (n=11) and 59.7% by week 48 (n=10).

Cost Comparison (Annual WAC)			
Patient Weight	**Epidiolex®***	**Fintepla®****	**Ztalmy®**
15 kg	$16,883	$81,266	$152,112
25 kg	$28,105	$135,144	$253,520
35 kg	$39,347	$189,621	$289,737
80 kg	$89,936	$201,231	$289,737

*Daily dose of 20 mg/kg
**Daily dose of 0.7 mg/kg and maximum dose of 26 mg

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Prescribed by or in consultation with a neurologist or other specialist in the treated disease state **AND**
- Documented diagnosis of cyclin-dependent kinase-like 5 deficiency disorder (ICD-10: G40.42) **AND**
- Documentation of genetic testing confirming presence of pathogenic or likely pathogenic variant in the *CDKL5* gene **AND**
- Participant aged 2 years or older **AND**
- Documented therapeutic trial of ≥ 2 prior antiepileptic therapies in the past 2 years (trial defined as two claims per HICL) (i.e., clobazam, felbamate, lamotrigine, levetiracetam, rufinamide, topiramate, valproate, vigabatrin, cannabidiol) **AND**
- Claim does not exceed maximum dosage limitations:
  - For participants weighing ≤ 28 kg: 63 mg/kg/day
  - For participants weighing > 28 kg: 1,800 mg/day **AND**
- Documentation of baseline monthly seizure frequency
- Initial approval: 6 months

Continuation of Therapy:

- Documentation of reduced seizure burden or improvement in quality of life using a validated scale for the disease state
- Continued approval: 12 months

Additional Provider Diagnostic/Monitoring Criteria, if desired:

- Monitor patients for somnolence and sedation and avoid concomitant use with other CNS depressants.
- Monitor patients for emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.
- Monitor patients with impaired hepatic function for the incidence of adverse reactions.

Implication to State Medicaid Program:

Estimated LOE: 9/18/2029

- Marinus estimates that there are about 2,000 patients who are eligible for treatment with Ztalmy.
- Ztalmy was previously being studied to control adult focal onset seizures, but it failed to show improvement over placebo in a Phase III trial.
- Off-label utilization is anticipated seeing as the pathogenic variant responsible for CDD has also been identified in many other conditions such as infantile spasms, West Syndrome, Lennox-Gastaut Syndrome, Rett Syndrome, cerebral palsy, autism, and intractable epilepsy of unknown origin.

Pipeline Therapies				
Product	**Route**	**MOA**	**Indication**	**Notes**
Ztalmy® (ganaxolone) [Marinus]	Oral	GABA receptor agonist	• LGS • TSC	
Ztalmy® (ganaxolone) [Marinus]	IV	GABA receptor agonist	• Refractory status epilepticus	Being studied in patients with status epilepticus refractory to two other drugs, as adjunctive therapy after failure of one drug, and in patients with established status epilepticus earlier in their disease continuum after failure of a benzodiazepine drug in the emergency department setting
Fintepla® (fenfluramine) [UCB]	Oral	Serotonin reuptake inhibitor	• CDD • Epileptic encepha-lopathy • Sunflower syndrome	Study in six patients with CDD whose seizures had failed 5-12 ASMs or therapies. Among 5 patients with tonic-clonic seizures, fenfluramine resulted in a median 90% reduction in frequency. Tonic seizure frequency was reduced by 50-60% in 2 patients
Soticlestat (OV935) (previously TAK-935) [Takeda]	Oral	Cholesterol synthesis inhibitor	• CDD • Dravet syndrome • LGS	Phase 2 ELEKTRA trial enrolled patients aged 2-17, 51 with Dravet syndrome and 88 with LGS to evaluate improvement of baseline seizure frequency of soticlestat versus placebo. Median placebo-adjusted seizure frequency reduced by 46% in patients with Dravet syndrome and 14.8% in patients with LGS.
Translarna™ (ataluren) [PTC Therapeutics]	Oral	Inhibitor of premature protein translation termination	• Aniridia • Becker muscular dystrophy • Dravet syndrome • Duchenne muscular dystrophy	No difference was found between ataluren and placebo; determined to not be an effective therapy for seizures or other disorders in children with Dravet syndrome or CDD due to nonsense variants

ASM = antiseizure medications; CDD = cyclin-dependent kinase-like 5 deficiency disorder; IV = intravenous; LGS = Lennox-Gastaut Syndrome; MOA = mechanism of action; TSC = Tuberous sclerosis complex

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