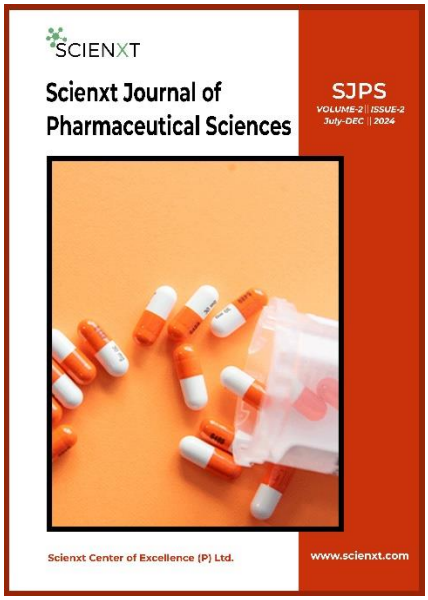


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# *A novel FDA approved drug*

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## Abstract:

Seizures can manifest with a wide range of symptoms, including temporary changes in muscle tone or movement, such as stiffness, twitching, or limpness, as well as alterations in behavior, sensation, or consciousness. These manifestations occur due to spontaneous and uncontrolled electrical impulses among neurons in the brain. This rare neurodevelopmental disorder, known as Cyclin-dependent kinase-like 5 deficiency disorder (CDKL5-DD), is characterized by severe epileptic encephalopathy, developmental delay, and intellectual disability. There is a lack of effective treatments for CDKL5-DD, despite significant research efforts. Ganaxolone, a synthetic analog of the neurosteroid allopregnanolone, is a potential therapeutic option with a mechanism of action that focuses on gamma-aminobutyric acid (GABA) receptors. These receptors are important for regulating neuronal excitability.

## Keywords:

Seizures, Cyclin- dependent- kinase- like 5 deficiency disorder, ZTALMY (Ganaxolone).

# 1. Introduction:

## 1.1. Seizure:

Seizures happen when there is an abrupt and uncontrollable surge of electrical activity in the brain, leading to changes in behavior, movements, emotions, and consciousness levels. Epilepsy is typically diagnosed when a person has two or more seizures that occur at least 24 hours apart, without a known cause. Seizures can manifest in different forms, with each type having distinct origins in the brain and varying degrees of spread. The symptoms and severity of these episodes can vary, usually lasting for a short duration of 30 seconds to two minutes. If a seizure lasts for more than five minutes, it is considered a medical emergency. Seizures can be triggered by a range of factors, including strokes, head injuries, infections like meningitis, or other illnesses. Nevertheless, in numerous instances, the precise cause remains unknown. While medication can effectively control most seizures, its use may have an impact on daily life. Working together with healthcare professionals is essential for finding a balance between controlling seizures and effectively managing any side effects caused by medication.

# 2. Cyclin-dependent kinase-like 5 deficiency disorder:

Cyclin-Dependent Kinase-Like 5 Deficiency Disorder (CDKL5-DD) is a rare and complex neurological condition that poses significant challenges in terms of diagnosis, management, and treatment. This condition, which involves mutations in the CDKL5 gene found on the X chromosome, primarily impacts females, although there have been a few documented instances in males. In recent years, extensive research has been conducted to understand the complex mechanisms involved in CDKL5-DD. This has provided valuable insights into the various clinical manifestations of the condition and potential treatment options. This review delves into the current understanding of CDKL5-DD, exploring its genetic basis, clinical presentation, diagnostic approaches, and available treatment options. This paper aims to offer a comprehensive overview of CDKL5-DD, synthesizing existing knowledge and highlighting recent advancements in the field. Its goal is to provide clinicians, researchers, and caregivers with valuable insights that can contribute to improved care and management strategies for individuals affected by this challenging disorder.

# 3. Ztalmy (Ganaxolone):

Marinus Pharmaceuticals, Inc. (Nasdaq: MRNS), a pharmaceutical company specializing in the development of groundbreaking therapies for seizure disorders, has recently received approval from the US Food and Drug Administration (FDA) for ZTALMY (Ganaxolone). ZTALMY is the first treatment approved by the FDA for seizures associated with Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients aged two and above. ZTALMY, an oral suspension of Ganaxolone, should be taken three times a day with food. The approval of ZTALMY in CDD by the FDA is based on the Phase 3 Marigold trial, which was a double-blind, placebo-controlled study with 101 patients. The results indicated that patients who received ZTALMY saw a significant decrease in major motor seizure frequency over a 28-day period, with a median reduction of 30.7%. In comparison, those who were given a placebo only experienced a median reduction of 6.9%. These findings successfully met the primary goals of the trial (p= 0.0036). In the Marigold open-label extension study, patients who received treatment with ZTALMY for a minimum of 12 months (n=48) experienced a significant decrease of 49.6% in the frequency of major motor seizures. During the clinical development program, ZTALMY showed effectiveness, safety, and tolerability. The most frequent side effects in the ZTALMY group were fever, excessive saliva production, and seasonal allergies, occurring in more than 15% of patients and at a rate at least twice that of the placebo. The approval of ZTALMY is a major achievement for the CDD community. It provides the first approved treatment option for CDD patients and brings renewed hope to those who have been searching for effective interventions to reduce daily seizure occurrences. The commercial availability of ZTALMY in the US is anticipated for July, pending scheduling by the US Drug Enforcement Administration. ZTALMY underwent a thorough review by the FDA, which resulted in the granting of orphan drug and rare pediatric disease designations. These designations are specifically for the treatment of CDD. In addition, Marinus has been granted a rare pediatric disease Priority Review Voucher (PRV) by the FDA, which the company intends to monetize.

## 4. Structure of ganaxolone (Ztalmy):

ZTALMY, the inaugural FDA-approved drug, is tailored for addressing seizures linked to Cyclin-dependent-kinase-like 5 deficiency disorder (CDD) among patients aged two years and above. This neuroactive steroid functions as a favorable modulator of the GABA receptor through allosteric activation, necessitating ingestion three times daily.

Molecular Formula = C22 H36 O2

Molecular Weight = 332.6 g/mol

## 5. Machanism of action of ganaxolone:

Seizures can be stopped by either decreasing excitement or increasing inhibition in the brain. GABA, the main inhibitory neurotransmitter, interacts with GABA a receptors, which promote the influx of negatively charged chloride ions into cells, resulting in a reduction in neuron activity. Ganaxolone, a man-made neuroactive steroid, acts as a positive allosteric modulator, enhancing the inhibitory effects of GABA. Ganaxolone enhances inhibitory signals by binding to specific locations on both intra- and extra-synaptic GABA a receptors. During prolonged or uncontrolled seizures, the presence of GABA receptors in the synapse is usually decreased, resulting in a reduced availability of these receptors. Nevertheless, extrasynaptic receptors sustain their functionality even after multiple instances of neuron firing. The activation of Ganaxolone at both types of receptors has the potential to strengthen inhibitory signals during seizures that last for a long time. Although the mechanism of Ganaxolone is not yet fully understood and is still being studied, it shows potential for effectively controlling acute seizures and chronic epileptic disorders.

## 6. Clinical pharmacology:

### 6.1. Mechanism of action:

The exact mechanism through which ganaxolone produces its therapeutic effects in treating seizures associated with CDD remains unclear, but it is believed to exert its anticonvulsant effects by positively modulating the gamma-aminobutyric acid type A (GABAA) receptor in the central nervous system (CNS).

### 6.2. Pharmacodynamics:

No pertinent information is available regarding the pharmacodynamic effects of ganaxolone.

### 6.3. Pharmacokinetics:

Regarding pharmacokinetics, ganaxolone is absorbed after oral administration of ZTALMY, with a peak plasma concentration (Tmax) typically occurring 2 to 3 hours post-dose. Administration with a high-fat meal significantly increases maximum plasma concentration

(Cmax) and area under the curve (AUC) compared to fasting conditions. Ganaxolone is highly protein-bound in serum, with a terminal half-life of approximately 34 hours. It is metabolized primarily by enzymes such as CYP3A4/5, CYP2B6, CYP2C19, and CYP2D6, with minor renal excretion.

## 6.4. Patient compliance:

There is no expected clinically relevant impact of age, sex, or race on ganaxolone pharmacokinetics when adjusted for body weight. Pediatric patients across different age groups exhibited comparable pharmacokinetic profiles. Renal impairment is unlikely to significantly affect ganaxolone exposure due to its minor renal excretion pathway. However, hepatic impairment is expected to increase ganaxolone exposure due to its hepatic clearance route.

## 6.5. In-vitro studies:

In vitro studies show that ganaxolone does not inhibit or induce various enzymes or transporters at clinically relevant concentrations. In vivo studies indicate that strong inducers or inhibitors of CYP3A4 can significantly affect ganaxolone exposure, while the effects of moderate or weak CYP3A4 inducers or inhibitors are not expected to be clinically significant.

# 7. Non-clinical pharmacology:

No carcinogenicity studies have been conducted on ganaxolone. It showed no genotoxicity in vitro but was associated with clastogenicity in an in vitro mammalian chromosomal aberration test. Ganaxolone did not impair fertility in rats at doses resulting in plasma exposures lower than those observed in humans at the maximum recommended dose.

## 7.1. Clinical trial data:

ZTALMY's efficacy in treating seizures associated with CDD in patients aged 2 years and older was demonstrated through a rigorous clinical trial, known as Study 1 (NCT03572933), which was conducted in a double-blind, randomized, and placebo-controlled manner. This study included patients aged 2 to 19 years who had confirmed molecular evidence of a pathogenic or likely pathogenic mutation in the CDKL5 gene. These patients had experienced inadequate seizure control despite undergoing at least two prior treatment regimens and were experiencing a minimum of 16 major motor seizures per 28 days prior to screening.

In Study 1, patients were randomly assigned in a 1:1 ratio to receive either ZTALMY or a placebo. After a 21-day titration period, patients in the ZTALMY group weighing 28 kg or less were administered a maintenance dosage of 21 mg/kg three times daily (with a maximum daily dose of 1800 mg), while those weighing more than 28 kg received a maintenance dosage of 600 mg three times daily.

Most patients (96%) were concurrently taking between 1 to 4 other antiepileptic drugs (AEDs). The commonly used concomitant AEDs included valproate (42%), levetiracetam (32%), clobazam (29%), and vigabatrin (24%).

The primary measure of effectiveness was the percentage change in the frequency of major motor seizures over a 28-day period compared to a 6-week prospective baseline phase during the 17-week double-blind phase. Results showed that patients treated with ZTALMY experienced a significantly greater reduction in the frequency of major motor seizures compared to those receiving the placebo.

## 8. Patient counselling data:

It's important for patients to carefully review the FDA-approved patient labeling, including the Medication Guide and Instructions for Use.

### 8.1. Somnolence and sedation:

Patients should be cautious about operating machinery, including driving, until they are confident that ZTALMY does not impair their judgment, thinking, or motor skills.

### 8.2. Suicidal thinking and behavior:

Patients, along with their caregivers and families, need to understand that antiepileptic drugs like ZTALMY may increase the risk of suicidal thoughts and behavior. They should be watchful for any signs of depression, mood changes, or thoughts of self-harm and report them promptly to healthcare providers.

### 8.3. Withdrawal of antiepileptic drugs (AEDs):

Patients should not stop using ZTALMY without consulting their healthcare provider. Gradual withdrawal is typically recommended to minimize the risk of increased seizure frequency.

### 8.4. Administration information:

Patients prescribed ZTALMY should use the adaptor and oral dosing syringes provided by their pharmacist. ZTALMY should be taken with food, and patients should shake the solution thoroughly before measuring each dose. Unused oral solution should be discarded after 30 days of opening the bottle.

## 8.5. Pregnancy registry:

Patients should inform their healthcare provider if they become pregnant or plan to during ZTALMY therapy. Women taking ZTALMY should consider enrolling in the North American Antiepileptic Drug (NAAED) Pregnancy Registry to contribute to the understanding of antiepileptic drug safety during pregnancy.

## 8.6. Potential for abuse:

Patients should be aware that ZTALMY carries the potential for abuse or dependence.

## 9. Prescribing information:

| | |
|---|---|
| Indication and Usage | Used in the treatment of seizures associated with Cyclin dependent kinase like (CDKL 5) deficiency disorder (CDD) |
| Administration | Administared by mouth 3 times daily and must be taken with food |
| Dose | 50mg/ml |
| Dosage form | Oral suspension |
| Contra indication | None |
| Warning | Somnolence and sedation, sucidal behaviour and ideation, withdrawl of antiseptic drugs |
| Adverse reaction | Somnolence, Pyrexia, salivary hypersecreation and seasonal allergy |
| Drug interaction | Cytochrome P450 |
| Population | Pregnancy, Lactation, Pediatric, Hepatic impairment |

## 10. Conclusion:

The research findings suggest that ZTALMY, a newly approved medicine by the FDA, effectively treats seizures in children between the ages of 2 and 17 who have been diagnosed with Cyclin dependent kinase like (CDKL 5) deficient disease. This is the first time that the FDA has officially approved a medication for seizures in this particular group of patients. To summarize, this review study provides insight into Cyclin-dependent kinase-like 5 deficient condition (ZTALMY) and the possible therapeutic use of Ganaxolone in treating it. By examining the fundamental processes and current methods of treatment, it becomes clear that Ganaxolone shows potential as a new therapeutic agent, providing hope for persons impacted by this difficult condition. However, additional investigation and rigorous testing are necessary to completely clarify its effectiveness, safety characteristics, and long-term results. By persistently pursuing scientific investigation and fostering collaboration among researchers, physicians, and pharmaceutical producers, we can work towards enhancing the well-being of individuals affected by ZTALMY and pushing forward the field of neurodevelopmental diseases.

## 11. Acknowledgement:

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### 11.2. Conflict of interest: None