

ZTALMY®

Category:

Best Product for Orphan/Rare Diseases

Company Name:

Marinus Pharmaceuticals

Product/Solution Name:

ZTALMY®

Compound/Tech Name:

(ganaxolone) oral suspension, CV

Trade Name:

Nasdaq: MRNS

Corporate Name:

Marinus Pharmaceuticals

Date of Approval:

2022-03-18

Indications:

Treatment of seizures associated with CDKL5 deficiency disorder (CDD), in patients 2 years of age and older.

Therapeutic Areas:

Epilepsy, Rare Disease

General Information File Document upload:

N/A

Background information and need for drug / device:

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare, X-linked developmental epileptic encephalopathy caused by CDKL5 gene mutations. The CDKL5 gene is responsible for making proteins that are important for normal brain functioning and development.

Previously known as serine/threonine protein kinase 9 (STK9), CDKL5 stands for cyclin-dependent kinase-like 5 and variants in this gene were first identified as disease-causing in 2004. Although rare, the incidence of CDD is believed to be between 1 in 40,000-60,000 live births, making it one of the most common genetic forms of epilepsy. Many cases have been identified in boys, but because of the location of the gene, CDD mainly affects girls.

ZTALMY® is the first and only treatment indicated for the treatment of seizures associated with CDKL5 deficiency disorder in people 2 years of age and older. Studied specifically in children and young adults with CDD ages 2 to 19, ZTALMY® has been proven to reduce the frequency of seizures associated with CDD.

Background File Document upload:

N/A

History of the development of the solution/product:

Patients diagnosed with CDD typically have infantile-onset epilepsy that responds poorly to currently available treatments. Other symptoms include hypotonia (poor muscle tone), severe developmental and cognitive delays with little or no speech production, fine and gross motor impairment (including inability to walk for most patients), cortical visual impairment, behavioral abnormalities, and sleep and digestive difficulties.

The effectiveness of ZTALMY ® to treat seizures associated with CDD in patients 2 years of age and older was established in a double-blind, randomized, placebo-controlled study in participants aged 2 to 19 years of age.

Participants had confirmed CDKL5 gene mutations, seizures inadequately controlled by at least two previous treatment regimens, and a minimum average of 16 major motor (convulsive) seizures per 28 days during a two-month period prior to screening.

Participants were mostly female (79%; consistent with CDD demographics), and 96% were also receiving other drugs to treat their seizures at the baseline (beginning) of the study. The most common other drugs were valproate, levetiracetam, clobazam, and vigabatrin.

To determine if the treatment worked, the effect of ZTALMY ® was evaluated based on

the percentage change in the 28-day frequency of major motor seizures from a 6-week prospective baseline phase during the 17-week double-blind treatment phase. At the end of the treatment phase, participants treated with ZTALMY® had a 31% median reduction in 28-day frequency of major motor seizures, compared to a 7% reduction for those receiving the placebo, a statistically significant difference.

ZTALMY® also reduced the frequency of seizures by at least half for some study participants. One in 4 participants taking ZTALMY® had at least a 50% reduction in frequency of seizures, compared to 1 in 10 participants taking the placebo.

101 children and young adults with treatment-resistant seizures associated with CDD, aged 2 to 19 years, participated in the clinical study. Participants had previously tried and discontinued between 1 and 16 seizure medicines. Participants were taking on average 2 to 3 seizure medicines and were still having frequent seizures. Seizure types that were assessed included bilateral tonic, generalized tonic-clonic, bilateral clonic, atonic, and focal to bilateral tonic-clonic.

In 2022, Marinus Pharmaceuticals received U.S. FDA approval for ZTALMY® (ganaxolone) oral suspension, making the product the first FDA approved treatment specifically in CDD using a neuroactive steroid that acts as a positive allosteric modulator of the GABAA receptor.

A recent long-term open-label extension study of ganaxalone included patients who completed the first phase of the study where they received ganaxalone or a placebo. Findings revealed that after two years, the 50 patients still being treated had about half as many seizures per month than their baseline (48% fewer seizures). For these same 50 patients, nearly half (46%) had more than half of their seizures stop and about a quarter (24%) of patients had a drop of more than 3/4 of the number of seizures that they had at baseline. Patients also had 4 more days per month without any seizures.

Development File Document upload:

N/A

Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition:

The cause of CDKL5 deficiency disorder remains unknown, with mutations having been found in children diagnosed with Infantile Spasms, West Syndrome, Lennox-Gastaut, Rett Syndrome, cerebral palsy, autism, and intractable epilepsy of unknown origin.

Additionally, the exact cause of seizures in CDD, as with other epilepsies, is not fully known. It is hypothesized that seizures may result from an imbalance of excitatory

(stimulating) and inhibitory (calming) signals in the brain.

Researchers have identified that gamma-aminobutyric acid, known as GABA, is the main inhibitory neurotransmitter which plays an important role in sending inhibitory signals to calm excited neurons (nerve cells). GABA sends inhibitory signals by attaching to certain GABA receptors found on neurons.

Depending on their location, some of the GABA receptors produce short bursts of inhibition, while others produce steady currents of inhibition. However, when these signals do not work as they should, neurons may become overexcited, causing seizures.

ZTALMY® is the first seizure medicine that is a neuroactive steroid, as well as the first treatment for seizures associated with CDD, and the first treatment specifically for CDD. Although it is not fully understood how ZTALMY works to treat seizures in CDD, it is thought to reduce seizures by enhancing the activity of GABA in the brain.

ZTALMY® enhances both types of inhibition by working on certain GABA receptors in different locations on the neuron. This dual approach may assist with the body's ability to calm overexcited neurons, thus reducing the likelihood of a seizure.

As the demand for research and treatment solutions for CDD has subsequently grown over the years, the development and application of ZTALMY® stands out as an innovative approach to anti-seizure treatment options. Patients and their families have shared the notable improvement to quality of life having had fewer seizures to manage on a weekly basis.

ZTALMY® was manufactured to closely align with the needs of pediatric patients. The oral medicine is sugar-free, cherry-flavored, and suitable for ketogenic diets. ZTALMY® does not require refrigeration which further increases suitability to a variety of daily environments.

Marinus Pharmaceuticals' further initiated ZTALMY® One, a comprehensive support program for patients and their families to use as part of the treatment plans for those prescribed ZTALMY. The program features useful resources, support, and educational tools that may be used to enhance the patient treatment journey.

As Marinus Pharmaceuticals explores other potential indications for ZTALMY® in alternative treatment areas, the scope for ZTALMY® offers additional benefits to the future of epilepsy research, such as the treatment of tuberous sclerosis complex which is a rare genetic disease that often causes seizures.

Innovation File Document upload:

N/A

Please provide appropriate references (PubMed, Abstract, Website):

Phase 3 Marigold data published in The Lancet Neurology:

[https://www.thelancet.com/journals/laneur/article/PIIS1474-4422\(22\)00077-1/abstract](https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(22)00077-1/abstract)

Marigold open label extension data published in Epilepsia:

<https://onlinelibrary.wiley.com/doi/10.1111/epi.17826>

ZTALMY website - Homepage: <https://www.ztalmy.com/>

ZTALMY website - Seizures in CDD: <https://www.ztalmy.com/seizures-cdd/>

ZTALMY website - About Ztalmy: <https://www.ztalmy.com/about-ztalmy/>

International Consensus Recommendations for the Assessment and Management of Individuals with CDKL5 Deficiency Disorder:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9251467/pdf/fneur-13-874695.pdf>

National Organization for Rare Disorders - CDKL5 Deficiency Disorder:

<https://rarediseases.org/rare-diseases/cdkl5/>

References File Document upload:

N/A