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A review and research on Lenmeldy

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- **Abstract:**

- **Lenmeldy Tablet and Intravenous infusion:**

In Europe, Lenmeldy is also known as Libmeldy, where it has been approved by the European Commission (EC), UK Medicines and Healthcare products Regulatory Agency (MHRA) and Swiss Agency for Therapeutic Products. Lenmeldy is indicated for the treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy. Lenmeldy is a gene therapy used to treat types of metachromatic leukodystrophy in children. It is world's new most expensive drug. Lenmeldy tablet is a mainly used in the treatment of neurological disorders, like epilepsy. It contains a combination of active ingredients designed to modulate neuronal activity and reduce seizure frequency in patients with refractory epilepsy.
This is the first FDA-approved treatment option for children who have this rare genetic disease.

-Proper Name: atidarsagene autotemcel

-Trade Name: LENMELDY

-Manufacture: Orchard Therapeutics (Europe) Limited

➢ **Keywords:**

Lenmeldy, metachromatic leukodystrophy, epilepsy, gene therapy.

Introduction:

Lenmeldy tablet is a pharmaceutical product primarily used for the treatment of epilepsy, a neurological disorder characterized by recurrent seizures. Here are key details about Lenmeldy tablet:

1. **Composition:** The active ingredient of Lenmeldy tablet is levetiracetam. Levetiracetam belongs to a class of medications known as antiepileptic drugs (AEDs). It is chemically described as (-)-(S)-alpha-ethyl-2-oxo-1-pyrrolidine acetamide.

2. **Indications:** Lenmeldy is indicated for the treatment of various types of seizures associated with epilepsy. This includes:

- Partial-onset seizures (focal seizures) with or without secondary generalization.
- Myoclonic seizures in patients with juvenile myoclonic epilepsy.
- Primary generalized tonic-clonic seizures.

3. **Mechanism of Action:** Levetiracetam, the active ingredient in Lenmeldy, works by binding to synaptic vesicle protein 2A (SV2A) in the brain. This modulates neurotransmitter release and neuronal excitability, thereby reducing the occurrence of seizures.

4. **Dosage:** The dosage of Lenmeldy varies depending on factors such as the patient's age, weight, renal function, and the type of seizures being treated. It is typically administered orally in tablet form and can be taken with or without food.

5. **Administration:** Lenmeldy tablets are usually taken once or twice daily, as prescribed by a healthcare provider. It is important for patients to adhere to the prescribed dosage schedule to maintain consistent therapeutic levels in the body.

6. **Side Effects:** Common side effects of Lenmeldy may include:

- Mouth sore
- Drowsiness
- Dizziness
- Weakness
- Gastrointestinal infections
- Fatigue

- Viral infections

Serious side effects are rare but may include behavioral changes, severe allergic reactions, and skin reactions.

7. Safety Considerations: Lenmeldy should be used with caution in patients with impaired renal function, as dosage adjustments may be necessary. Regular monitoring of renal function is recommended during treatment.

8. Drug Interactions: Lenmeldy may interact with other medications, including other antiepileptic drugs and certain antibiotics. It is important for healthcare providers to review the patient's complete medication history to avoid incompatibilities, potential interactions.

9. Pregnancy and Lactation: The safety of Lenmeldy during pregnancy and breastfeeding is not well-established. Healthcare providers should weigh the potential benefits and risks before prescribing this medication to pregnant or breastfeeding women.

10. Patient Counseling: Patients taking Lenmeldy should be educated about the importance of adherence to prescribed dosages, regular follow-up visits with healthcare providers, and recognition of potential side effects. They should also be informed about what to do in case of missed doses or any unusual symptoms.

Lenmeldy tablet is a valuable treatment option for patients with epilepsy, providing effective seizure control when used as prescribed and monitored by healthcare professionals.

- ## Objectives:

The objectives of Lenmeldy tablet has therapeutic use in the treatment of epilepsy. Primary objectives are as follows:

1. Seizure Control: The main objective of Lenmeldy tablet is to reduce the frequency, severity, and duration of seizures in patients with epilepsy. It aims to stabilize neuronal activity in the brain, by preventing the abnormal electrical discharges that leads to seizures.

2. Management of Different Seizure Types: Lenmeldy is designed to address various types of seizures associated with epilepsy, including partial-onset seizures (focal seizures), myoclonic seizures in juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures. By targeting multiple seizure types, it provides comprehensive management for epilepsy patients.

3. Improvement in Quality of Life: Effective seizure control with Lenmeldy tablet improves the quality of life for individuals with epilepsy. By minimizing the impact of seizures, it helps patients

to maintain the normal daily activities, reduces the risk of injury during seizures, and enhances overall well-being.

4. Long-term Treatment Stability: Another objective is to provide a stable, long-term treatment option for epilepsy management. Lenmeldy tablet offers convenient oral administration, allowing for consistent therapeutic levels in the body when taken as prescribed.

5. Safety and Tolerability: Ensuring safety and tolerability is crucial. Lenmeldy aims to provide an acceptable side effect profile, balancing efficacy with minimized adverse effects. Healthcare providers monitor patients for potential side effects, especially during the initial titration period and dose adjustments.

Lenmeldy tablet objectives include educating patients about the importance of medication adherence. Patients are counseled on the significance of taking the medication regularly as prescribed to maintain effective seizure control and to minimize risks associated with uncontrolled epilepsy.

Overall, the objectives of Lenmeldy tablet align with providing effective seizure management, improving patient outcomes, ensuring safety, and enhancing the quality of life for individuals living with epilepsy.

- **What is Lenmeldy:**

Lenmeldy is a one-time, individualized single-dose infusion made from the patients own hematopoietic (blood) steam cells (HSCs)

- Product Information:

Package Insert - LENMELDY Support Documents
March 18, 2024 Approval Letter - LENMELDY
March 18, 2024 Summary Basis for Regulatory Action - LENMELDY Approval History, Letters, Reviews, and Related Documents - LENMELDY
physical and neurological examinations, ordering imaging scans such as MRI (magnetic resonance imaging) or CT (computed tomography), and other laboratory tests.

- Orchard Therapeutics revealed details regarding the U.S. commercial launch of the newly approved Lenmeldy (atidarsagene autotemcel), giving the one-time gene therapy for metachromatic leukodystrophy a wholesale acquisition cost of $4.25 million.

- **What are the treatments for leukodystrophies?**

There is no cure for leukodystrophies. Treatment focuses on relieving symptoms and providing support. It may include:

- Medicines to manage muscle tone, seizures, and spasticity (muscle stiffness)

- Physical, occupational, and speech therapies to improve mobility, function, and cognitive problems

- Nutritional therapy for eating and swallowing problems

- Educational and recreational programs

- Stem cell or bone marrow transplantation can be helpful for a few types of leukodystrophy.

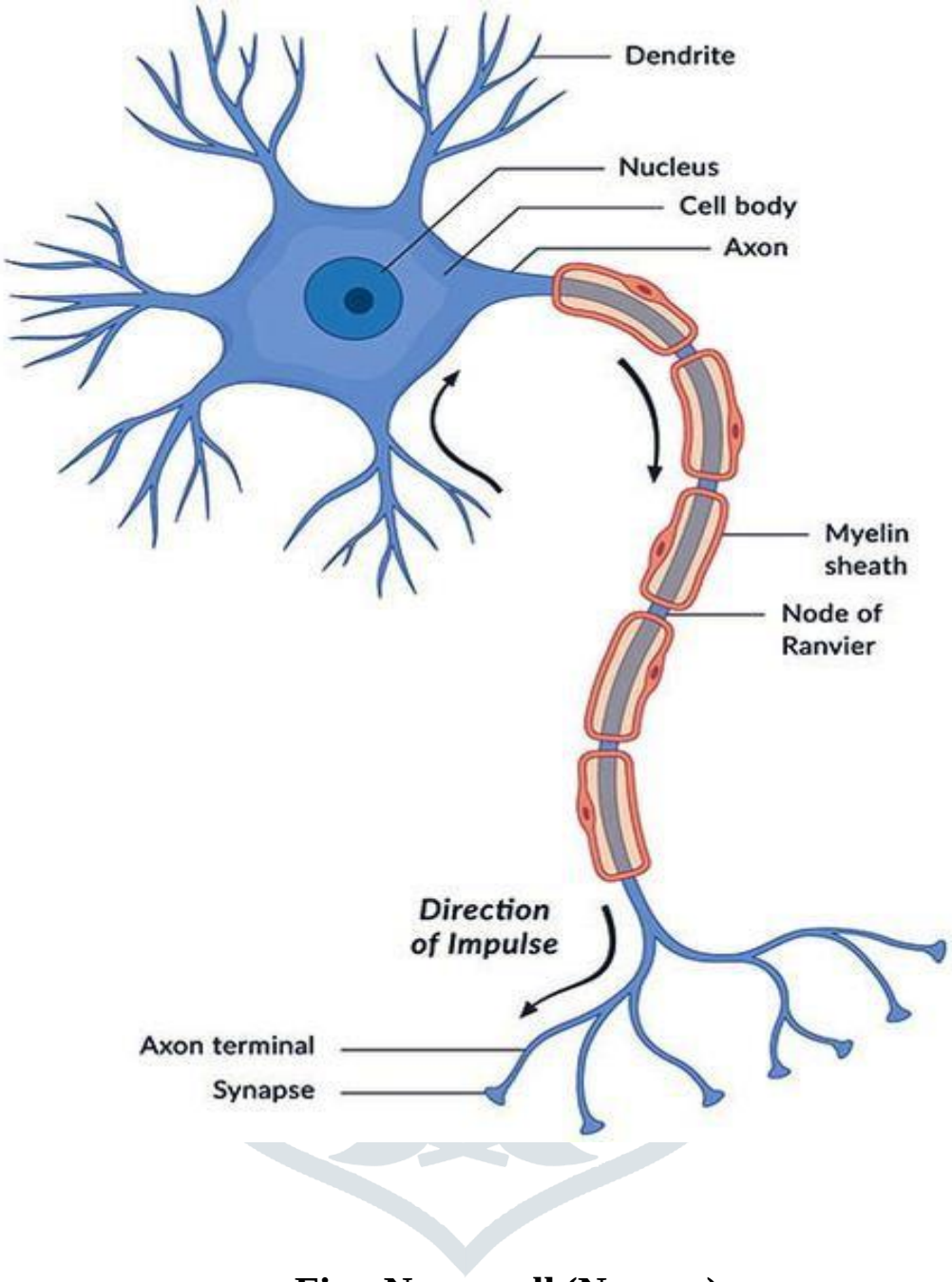
- **Metachromatic Leukodystrophy:**

- Metachromatic leukodystrophy is an inherited disorder characterized by the accumulation of fats called sulfatides in cells. This accumulation especially affects cells in the nervous system that produce myelin, the substance that insulates and protects nerves. Nerve cells covered by myelin make up a tissue called white matter. Sulfatide accumulation in myelin-producing cells causes progressive destruction of white matter (leukodystrophy) throughout the nervous system, including in the brain and spinal cord (the central nervous system) and the nerves connecting the brain and spinal cord to muscles and sensory cells that detect sensations such as touch, pain, heat, and sound (the peripheral nervous system). It's frequency is 1 in 40,000 births.

- The people that having metachromatic leukodystrophy disorder, it causes and damages progressive deterioration of intellectual functions and motor skills, such as the ability to walk. Affected individuals also develop loss of sensation in the extremities (peripheral neuropathy), incontinence, seizures, paralysis, an inability to speak, blindness, and hearing loss.

- The most common form of metachromatic leukodystrophy, affecting about 50 to 60 percent of all individuals with this disorder, is called the late infantile form. This form of the disorder usually appears in the second year of life. Affected children lose any speech they have developed, become weak, and develop problems with walking (gait disturbance). As the disorder worsens, muscle tone generally first decreases, and then increases to the point of rigidity. Individuals with the late infantile form of metachromatic leukodystrophy typically do not survive past childhood.

- Physical and neurological examinations, ordering imaging scans such as MRI (magnetic resonance imaging) or CT (computed tomography), and other laboratory tests, with the help of these tools, leukodystrophy can be difficult to diagnose. Doctors can use other specialized tests such as DNA sequencing to check for genetic disorders. Whole-exome and whole- genome sequencing tests that map out and analyze the genetic information contained in all of a person's genes often are used to identify and pinpoint specific genetic problems.



- **Fig.- Nerve cell (Neuron)**

- **Leukodystrophy:**

Leukodystrophy is used to describe a group of rare, primary inherited neurological disorders. It may affect the Central Nervous System and the neurons. It results from the abnormal production, processing, or the development of myelin and the other components of CNS white matter, such as cells called oligodendrocytes and astrocytes.

- **Treating leukodystrophy:**

Treatment for most types of leukodystrophy is symptomatic and supportive, and may include:

- Medications to manage muscle tone, seizures, and spasticity.
- Physical, occupational, and speech therapy to help improve mobility and function, and help people adapt to cognitive challenges.
- Nutritional, educational, and recreational programs
- Stem cell or bone marrow transplantation is showing promise for a few types of leukodystrophy. Research in this area is ongoing.

- **Symptoms are as follows:**

1) Muscle tone
2) Mobility, walking ability
3) Speech
4) Vision
5) Behavior
6) Learning disabilities
7) Bladder issues
8) Breathing problems
9) Muscle control disorders, seizures.

- **Mechanism of action of Lenmeldy:**

- Lenmeldy (atidarsagene autotemecel) inserts one or more functional copies of the human ARSA complementary deoxyribonucleic acid (cDNA) into the patients' HSCs through transduction of autologous CD34+ cells with ARSA LVV. After Lenmeldy infusion, transduced CD34+ HSCs engraft in bone marrow, repopulate the hematopoietic compartment and their progeny produce ARSA enzyme. Functional ARSA enzyme can breakdown or prevent the harmful accumulation of sulfatides.

- **Side effects of Lenmeldy:**

1)Febrile neutropenia 2)Stomatitis
3)Respiratory tract infection 4)Rashes
5) Device related infection
6) Other viral infection 7)Pyrexia 8)Gastroenteritis
9) Enlarged liver
10) Mouth sore
11) Low WBC count.

- ## What is epilepsy:

Epilepsy is also known as a seizure disorder. A seizure is a sudden, uncontrolled burst of electrical activity in the brain i.e. between brain cells (also called neurons and nerve cells). It can cause changes in behavior, movements, feelings, sensations and levels of consciousness in a person.

- ## Symptoms of epilepsy:

1)Temporary confusion
2)Stiff muscles
3)Loss of consciousness 4)Fear, anxiety
5)Uncontrollable jerking movements of the arms and legs.

- ## Types of epilepsy:

1)Focal onset epilepsy 2)Generalized onset epilepsy
3)Combined generalized
4)Focal epilepsy

- ## Gene Therapy:

1)A treatment in which the genes that are missing or not normal in your cells, are replaced with normal genes is known as Gene Therapy. Gene therapy is a technique that uses a gene to treat, prevent or cure the disease or medical disorder.

2)The Cellular, Tissue and Gene Therapies Advisory Committee reviews and evaluates available data relating to the safety, effectiveness, and appropriate use of human cells, human tissues, gene transfer therapies and xenotransplantation products which are intended for transplantation, implantation, infusion and transfer in the prevention and treatment of a broad spectrum of human diseases and in the reconstruction, repair or replacement of tissues for various conditions.

3)The Committee shall consist of a core of 13 voting members including the Chair. Members and the Chair are selected by the Commissioner or designee from among authorities knowledgeable in the fields of cellular therapies, tissue transplantation, gene transfer therapies and xenotransplantation including biostatistics, bioethics, hematology/oncology, human tissues and transplantation, reproductive medicine, general medicine and various medical specialties including surgery and oncology, immunology, virology, molecular biology, cell biology, developmental biology, tumor biology, biochemistry, rDNA technology, nuclear medicine, gene therapy, infectious diseases, and cellular kinetics.

4)Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. CBER has approved both cellular and gene therapy products – a list of these products may be found on the Approved Cellular and Gene Therapy Products webpage.

- Various types of gene therapy products includes are as follows:

1) Plasmid DNA
2) Viral vectors
3) Bacterial vectors
4) Human gene editing technology
5) Patient-derived cellular gene therapy products

- **Before taking this medicine:**

Before your child is given Lenmeldy, the doctor will:

1)Check your child's lungs, heart, kidney, liver and the blood pressure.
2)Checks that any infection will be treated before your child is given this medicine.
3)Check for hepatitis B, hepatitis C, human T-cell lymphotropic virus (HTLV), cytomegalovirus (CMV), HIV, or mycoplasm infection.

- **Interactions:**

- Vaccinations are not recommended during the 6 weeks before the start of myeloablative conditioning and until hematological recovery following treatment with Lenmeldy.

- Your child should not take any anti-retroviral medications for at least one month before the mobilization medicines or the expected duration for elimination of the medications as the anti-retroviral medications may interfere with the manufacturing of Lenmeldy.

- **Conclusion:**

- Lenmeldy tablet represents a valuable therapeutic option for patients suffering from epilepsy and related neurological disorders. Its efficacy in controlling seizures, coupled with an acceptable safety profile, makes it a cornerstone in epilepsy management.

- Lenmeldy tablet represents an important therapeutic option for managing epilepsy, a neurological condition characterized by recurrent seizures. Here are key points summarizing its significance:

1. Broad Indications: It is approved for treating partial-onset seizures (focal seizures) with or without

secondary generalization, myoclonic seizures in juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures. This broad spectrum of indications highlights its versatility in managing different forms of epilepsy.

2. Safety Profile: While generally well-tolerated, Lenmeldy may cause side effects such as drowsiness, dizziness, and fatigue. Serious adverse effects, although rare, require monitoring, particularly in patients with renal impairment. Careful dosing adjustments and regular renal function tests are essential for safe use.

3. Patient Compliance and Counseling: Patient education regarding the importance of adhering to prescribed dosages, recognizing potential side effects, and seeking medical advice promptly are crucial for optimizing treatment outcomes. Proper management under healthcare supervision helps mitigate risks and ensures effective seizure management.

4. Clinical Significance: Lenmeldy plays a significant role in improving the quality of life for epilepsy patients by providing reliable seizure control. Its mechanism of action and established efficacy make it a cornerstone in the treatment regimen, particularly for those with refractory or difficult-to-control seizures.

In essence, Lenmeldy tablet stands as a reliable and effective therapeutic option in the management of epilepsy, contributing to better seizure management and enhanced patient well-being under appropriate medical guidance.

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