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Givinostat: A New Frontier in the Treatment of Duchenne Muscular Dystrophy Review Article

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ABSTRACT:

Duchenne muscular dystrophy (DMD) is a rare and severe genetic condition that causes gradual muscle decreasing and deterioration. This comprehensive study examines the epidemiology, histology, etiology, symptoms, diagnosis, and therapy options for DMD. The study emphasises the need of early diagnosis and therapy, which includes the use of corticosteroids, exon-skipping medicines, and new treatments like as givinostat. Givinostat, a histone deacetylase inhibitor, has showed promise in clinical trials and has acquired FDA approval to treat DMD in individuals aged six and up.

Keywords: Duchenne muscular dystrophy (DMD), Givinostat, histone deacetylase inhibitor.

INTRODUCTION:

Duchenne muscular dystrophy (Duchenne) is a rare X-linked neuromuscular illness that affects about one in every 5,000 newborn men globally. Muscular dystrophies (MD) are prevalent neuromuscular (nerve and muscle) disorders that cause muscle strength and mass loss. Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy. Duchenne muscular dystrophy (DMD) is one of the most severe types of hereditary muscular dystrophies. Mutations in the dystropin gene cause increasing muscle weakness and loss of motor function, which is exacerbated by pulmonary and cardiac problems, resulting in mortality often in the third decade. The first indicator is discovered in early childhood (2 to 5 years), when the symptoms gradually increase and render the patient non-ambulatory.The distress associated with the Duchenne prognosis, progressive loss of function, and limitations in activities of daily living impact the quality of life of patients and their caregivers.

EPIDEMIOLOGY:

The epidemiologyof Duchenne muscular dystrophy (DMD) provides valuable insights into the disease's prevalence, incidence, and demographics.

Prevalence and incidence:

1. **Prevalence**: DMD is expected to affect 1 in 5,000 to 1 in 7,500 live male newborns.

2. **Incidence:** DMD is predicted to affect one in every 3,500 to 5,000 live male births.

Demographics:

1**. Gender:** Because DMD is an X-linked recessive condition, it affects mostly males.

2**. Age:** Symptoms typically appear in early childhood, between 2-5 years old.

3**. Ethnicity**: DMD affects all ethnic groups, with no significant variations in prevalence.

Geographic Distribution:

1. **Global distribution:** DMD is found worldwide, with no specific geographic clustering.

2. **Regional variations**: Some studies suggest regional variations in prevalence, but these findings are not conclusive.

Mortality and Survival:

1**. Life expectancy**: Without therapy, people with DMD typically have a life expectancy of 20 to 30 years.

2**. Mortality rates:** DMD patients die most frequently from respiratory and heart problems.

3**. Improved survival:** Advances in medical care and management have resulted in higher survival rates, with some people living into their 40s and 50s.

Genetic Epidemiology:

1. **Genetic mutations**: Inheritance accounts for roughly two-thirds of DMD cases, whereas spontaneous mutations account for the other one-third.
2. **Carrier frequency:** Female carriers of DMD mutations are expected to be between 1 in 50 and 1 in 100.

The epidemiology of DMD is critical for developing effective management techniques, enhancing patient care, and furthering research into this crippling disease.

PATHOLOGY:

The pathology of Duchenne muscular dystrophy (DMD) involves a complex interplay of cellular and molecular mechanisms that ultimately lead to muscle degeneration and weakness.

Muscle Pathology:

1.**Muscle fiber necrosis**: Necrosis of muscle fibres causes inflammation and the release of enzymes.

2. **Muscle fiber regeneration:** Regeneration of muscle fibers occurs, but it is incomplete and ineffective, leading to the formation of fibrotic tissue.

3. **Fibrosis:** The accumulation of fibrotic tissue replaces functional muscle tissue, contributing to muscle stiffness and weakness.

4. **Muscle fiber splitting:** Muscle fibers undergo splitting, leading to the formation of smaller, irregularly shaped fibers.

Pathology of Cells:

1. **Dystrophin deficiency:** Muscle cell membrane instability results from the lack or insufficiency of dystrophin, a protein essential to muscle function.

2. **Sarcolemmal damage**: When the sarcolemma, the membrane lining muscle cells, is destroyed, calcium ions enter the cell and proteolytic enzymes are activated.

3. **Inflammation:** Inflammation occurs, with the infiltration of immune cells, such as macrophages and T cells.

4. **Apoptosis:** Programmed cell death (apoptosis) occurs, contributing to muscle fiber loss.

Molecular Pathology:

1. **Dystrophin gene mutation**: When the dystrophin gene is mutated, the dystrophin protein is either absent or insufficient.

2. **Disruption of the dystrophin-glycoprotein complex:** Muscle cell membrane instability results from the disruption of the dystrophin-glycoprotein complex.

3. **Dysregulation of signalling pathways:** Loss and degeneration of muscle fibres are caused by the dysregulation of signalling pathways, such as the PI3K/Akt pathway.

Additional Pathological Characteristics:

1. **Cardiac involvement:** Cardiomyopathy and heart failure result from damage to the heart muscle.

2. **Involvement of the respiratory system:** Respiratory failure is caused by weak breathing muscles.

3. **Cognitive impairment**: Cognitive impairment and learning disabilities are common in DMD patients.

ETIOLOGY:

Duchenne muscular dystrophy (DMD) is predominantly a hereditary condition.

Basis in Genetics:

1. **Dystrophin gene mutation:** DMD is caused by mutations in the dystrophin gene (DMD), which is located on the X chromosome (Xp21.2).

2. **X-linked recessive inheritance:** The dystrophin gene mutation is inherited in an X-linked recessive pattern, meaning that the mutated gene is located on the X chromosome and a single copy of the mutated gene is sufficient to cause the condition.

3. **Frameshift mutations:** The most common type of mutation leading to DMD is a frameshift mutation, which results in a premature stop codon and a truncated, non-functional dystrophin protein.

Molecular Processes:

1. **Function of the dystrophin protein:** Dystrophin is a cytoskeletal protein that is essential for preserving the stability and integrity of muscle cell membranes.

2. **Dystrophin-glycoprotein complex:** Dystrophin interacts with other proteins to form the dystrophin-glycoprotein complex (DGC), which links the cytoskeleton to the extracellular matrix.

3**. Loss of dystrophin function:** The absence or deficiency of dystrophin leads to a disruption of the DGC, causing muscle cell membrane instability, inflammation, and eventually, muscle cell death.

Other Factors:

1. **Genetic modifiers:** Other genes, such as those involved in muscle growth and repair, may influence the severity and progression of DMD.

2. **Environmental factors:** Environmental factors, such as physical activity and nutrition, may also impact the progression of DMD.

However, the primary cause of DMD is the mutation in the dystrophin gene, which leads to the absence or deficiency of the dystrophin protein.

DYSTROPHIN:

One important protein that is essential for preserving the structure and functionality of muscle cells is dystrophin.

Structural Role:

1. **Cytoskeletal anchor:** Dystrophin provides mechanical stability and support by attaching the cytoskeleton to the sarcolemma, the membrane of muscle cells.

2. **Link to extracellular matrix:** Dystrophin connects the muscle cell to the surrounding tissue through interactions with the extracellular matrix. **Role in Function:**

1. **Muscle contraction and relaxation:** By interacting with other proteins involved in muscle function, dystrophin helps control muscular contraction and relaxation.

2. **Cell signalling**: Dystrophin influences the development, differentiation, and survival of muscle cells by taking part in cell signalling pathways.

3. **Protection of muscle cells:** By preserving the integrity of the muscle cell membrane, dystrophin shields muscle cells from mechanical stress and harm.

Dystrophin Deficiency's Effects:

1. **Damage to muscle cells:** In the absence of dystrophin, muscle cells are more prone to deterioration.

2. **Muscle weakness and wasting:** Duchenne muscular dystrophy (DMD) is characterised by increasing muscle weakness and wasting brought on by dystrophin deficiency.

3. **Muscle fibrosis**: This condition, in which effective muscle tissue is replaced by scar tissue, is facilitated by dystrophin deficiency.

CAUSES:

Dystrophin deficiency in the muscles of people with DMD is caused by a mutation in the dystrophin gene. It causes damage to the muscular fibres and causes the muscles to gradually deteriorate.

Genetic Factors:

1. **Point mutations:** A particular kind of genetic mutation known as a point mutation occurs when one nucleotide base in the DNA or RNA sequence changes. This alteration can manifest as a substitution of one base pair

2**. Deletions:** A deletion is a kind of mutation in genomics that occurs when one or more nucleotides are removed from a DNA sequence. Any number of nucleotides can be lost during a deletion, ranging from one nucleotide to a whole chromosome.

3.**Duplications:**In the context of genomics, duplication is a form of mutation that results in the production of one or more copies of a DNA segment, which can range in size from a few bases to a substantial chromosomal area. All creatures have duplications. For instance, they can cause genetic illnesses in humans, although they are particularly common in plants. A key mechanism in the evolution of human and other creatures' genomes has been duplication.

The pattern of inheritance for Duchenne muscular dystrophy (DMD) is known as X-linked recessive. This indicates that while females may be carriers, nearly all DMD patients are male.

X-Linked Recessive Inheritance:

1**. X-linked**: The DMD gene is located on the X chromosome.

2. **Affected individuals:** Almost all affected individuals with DMD are male. A single copy of the mutated gene is sufficient to cause the condition in males, who have only one X chromosome. 3.**Female carriers:** The mutant gene may be carried by females. Although the DMD gene is "carried" by the mother, it typically does not cause issues for the daughter, and it typically affects the boys. The 'faulty' DMD gene is present on one of the two X chromosomes found in females, whereas the normal gene on the other X chromosome makes up for the defective one. Because they lack a second X chromosome, sons with the DMD gene are unable to make up for the defective gene. As a result, sons who carry the DMD gene are always exhibiting signs of the illness.

Inheritance Risk:

A carrier mother's son has a 50% probability of inheriting the mutant gene and becoming impacted. Each daughter of a carrier mother has a 50% chance of inheriting the mutant gene and becoming a carrier herself. Although a carrier daughtermay have very minimal symptoms, they frequently don't become aware of their status until after the birth of an affected son.

Although extremely uncommon, female affectedness may arise if the father is afflicted and the mother is a carrier.

SYMPTOMS:

The symptoms of Duchenne muscular dystrophy (DMD) typically appear in early childhood and progress over time. Here are the common symptoms:

Early Symptoms (2-5 years):

1.**Delayed motor milestones:** Sitting, standing, and walking can all be delayed in children with DMD.

2. **Muscle weakness:** Deterioration of the shoulder, thigh, and hip muscles.

3. **Waddling gait:** A distinctive waddling motion brought on by weakened hip and thigh muscles.

4. **Frequent falls:** Children with DMD may experience frequent falls due to muscle weakness and poor balance.

Progressive Symptoms (5-10 years):

1.**Muscle wasting**: Progressive muscle wasting and loss of muscle mass.

2. **Loss of ambulation:** Children with DMD typically lose the ability to walk between 8-12 years old.

3. **Contractures**: Contractures (permanent muscle shortening) in the joints, leading to limited mobility.

4. **Scoliosis**: Progressive curvature of the spine.

Symptoms of the Late Stage (10+ years):

1**. Breathing failure:** This condition is caused by weakness in the breathing muscles.

2**. Cardiac complications:** Cardiomyopathy and heart failure due to muscle weakness and fibrosis.

3**. Cognitive impairment:** Some individuals with DMD may experience cognitive impairment and learning disabilities.

4. **Loss of upper limb function:** Progressive loss of upper limb function, making daily activities challenging.

Other Symptoms:

1. **Fatigue:** Fatigue and muscle tiredness.

2. **Pain:** Muscle pain and cramping.

3. **Digestive issues:** Gastrointestinal problems, such as constipation and delayed gastric emptying.

The severity and progression of symptoms can vary significantly among individuals with DMD.

DIAGNOSIS:

The diagnosisof Duchenne muscular dystrophy (DMD) involves a combination of clinical evaluation, laboratory tests, and genetic analysis.

Clinical Assessment:

1. **Medical history:** To determine the signs and course of muscle weakness, a comprehensive medical history is necessary.

2. **Physical examination:** A physical examination is used to evaluate reflexes, muscular tone, and strength.

3. **Neurological examination:** This test evaluates coordination, sensory function, and cognitive function.

Tests in the Lab:

1**. Creatine kinase (CK) levels**: Damage to muscles may be indicated by a higher CK level. Although a high CK level can lead to more testing, it is not a reliable diagnostic method.

2. **Liver function testing:** Muscle injury may be indicated by abnormal liver function tests.

3. **Electromyography (EMG):** EMG diagnoses muscular injury by measuring the electrical activity of muscles.

Analysis of Genetics:

1. **Genetic testing:** To find dystrophin gene mutations, genetic testing is used. The most reliable and conclusive way to diagnose DMD is through genetic testing. To find mutations or alterations in the dystrophin gene, a blood sample is analysed.

2. DNA sequencing: This method verifies whether a mutation is present.

3. **Genetic counselling:** Genetic counselling to talk about the risk of transmission to other family members and the ramifications of the diagnosis.

Additional Diagnostic Examinations:

1**. Muscle biopsy:** One method of detecting abnormalities in the muscles, such as the lack of dystrophin protein in the muscle fibres, which is a feature of DMD, is a muscle biopsy.

2**. Imaging studies:** Imaging tests to evaluate heart and muscle function, such as CT or MRI scans.

3**. Pulmonary function testing**: These tests evaluate the respiratory system.

Algorithm for Diagnostics:

1. **Clinical assessment and medical history:** preliminary assessment to determine the onset and course of muscle weakness.

2. **Genetic analysis and laboratory testing:** Genetic analysis and laboratory testing are used to validate the diagnosis.

3**. Other diagnostic tests:** Other diagnostic tests, such as muscle biopsy and imaging studies, to assess muscle and cardiac function.

TREATMENT:

The treatment of Duchenne muscular dystrophy (DMD) involves a multidisciplinary approach to manage the symptoms, slow disease progression, and improve quality of life.

Drugs:

1. **Corticosteroids:** To increase muscle strength and slow down muscle deterioration, prednisone and deflazacort are frequently administered. They can enhance the function and strength of muscles.

2. **Exon skipping therapies:** In order to restore dystrophin production, approved medications golodirsen (Vyondys 53) and eteplirsen (Exondys 51) skip particular exons.

3. **Heart drugs**: To treat heart problems, doctors may prescribe ACE inhibitors, beta blockers, and diuretics. The cardiac muscle may be impacted by DMD. Medication and routine cardiac monitoring may aid in the management of heart-related issues.

Rehabilitation and Physical Therapy:

1.**Physical therapy:** Regular exercise and physical therapy can help maintain muscle strength and mobility. It can help people with DMD optimize their physical abilities and reduce the risk of joint contractures.

2.**Orthotics and assistive technology**: Wheelchairs, braces, and other assistive technology can increase a person's independence and mobility.
3. **Respiratory therapy:** People with DMD may need respiratory support, such as mechanical ventilators or breathing assistance devices, as their disease worsens.

Surgical Procedures:

1. **Spinal surgery:** To treat spinal abnormalities, scoliosis surgery may be required.

2. **Cardiac surgery:** To treat cardiac problems, heart transplantation or other cardiac procedures might be necessary.

Supportive Care:

1.**Gene therapy:** To restore dystrophin production, researchers are investigating gene therapy techniques.

2. **Gene editing:** The ability of gene editing tools, such as CRISPR/Cas9, to fix mutations that cause DMD is being researched.

3. **Stem cell therapy:** The potential of stem cell therapies to replace or repair damaged muscle tissue is being investigated.

Exon-Skipping Therapy:

Exon-skipping therapy shows significant clinical promise for treating Duchenne muscular dystrophy (DMD). Evidence suggests that revertant fibers, which are rare dystrophin-positive fibers found in the muscles of DMD patients, arise when mutations are bypassed through exon skipping. This leads to the restoration of dystrophin expression. DMD phenotypes can vary, ranging from severe DMD (with a complete lack of dystrophin) to Becker muscular dystrophy (BMD) or even asymptomatic cases where truncated dystrophin proteins are produced. With recent advancements in artificial nucleic acids, highly efficient and relatively safe antisense oligonucleotides (AOs) have been developed for exon skipping, making this therapy a promising approach for DMD treatment.

AOs are synthetic DNA sequences, approximately 20 bases long, designed to bind complementary regions of target pre-mRNA. Various modified chemicals have been developed to enhance stability, specificity, and resistance to nucleases, while minimizing toxicity. Among these, 2′-O-methyl-phosphorothioate AOs (2′OMeAOs) and phosphorodiamidate morpholino oligomers (PMOs) are considered the most effective. Exon skipping works by influencing the spliceosome complex, which is responsible for splicing pre-mRNA. AOs are designed to bind to exon-intron boundaries or exon-splicing enhancers, blocking the spliceosome and promoting exon skipping. However, designing AOs is complex and requires optimization based on pre-mRNA secondary structures. When AOs hybridize with targeted exons, they induce exon skipping, correct the reading frame, and restore dystrophin expression. This method is applicable to about 90% of DMD cases, as multiple exon deletions can be targeted. Compared to other therapies like gene therapy or stem cell transplantation, AOs can be considered drugs, potentially reducing ethical concerns.

GIVINOSTAT:

An investigational medication called glinostat is being studied as a possible treatment for Duchenne muscular dystrophy (DMD), a severe and uncommon hereditary condition that impairs muscle function and strength. the management of DMD in patients who are at least six years old. The first nonsteroidal medication authorised to treat patients with all hereditary forms of DMD is glinostat.

Generic name: Givinostat

Brand name: Duvyzat○R

Manufacturer: ItalfarmacoSpA

FDA approval date: March 21, 2024

Drug class: Small molecule histone deacetylase inhibitor

Cost: As of the publication date, the commercial price for Duvyzat○R had not been determined. It is expected to be available in the third quarter of 2024.

Potential Benefits:

Research suggests that givinostat may offer several benefits, including:

1. **Better muscular function and strength:** Increased dystrophin synthesis may prevent or reduce the onset of muscle weakness.

2. **Reduced muscle inflammation**: Givinostat's anti-inflammatory properties may minimize muscle damage and inflammation.

3. **Enhanced muscle regeneration:** Promoting muscle cell growth and differentiation may aid in muscle regeneration.

Mechanism of action:

Histone deacetylation inhibitor

↓

Inhibitor the tightly wrapped DNA

↓Making it

Transcription factors to bind the DNA

↓ Leads to

Normal level of gene expression

Givinostat functions by preventing the activity of histone deacetylase enzymes since it is a histone deacetylase inhibitor (HDACi). HDAC inhibitor that lowers inflammation and muscle loss by focussing on harmful processes Muscular dystrophies have been reported to exhibit altered HDAC expression and activity, indicating a role for these enzymes in the disease's progression. Inhibiting these enzymes can boost the production of dystrophin, a protein necessary for muscle.

Recommended Evaluation

Recommended Evaluation And Testing Before Initiation O

Givinostat

- Evaluation the platelet counts and triglycerides prior to initiation of givinostat.

❖ Weight	❖ Dosage	❖ Oral suspension volume
❖ 10 Kg to less than 20 Kg	❖ 22.2 mg twice daily	❖ 2.5 mL twice daily
❖ 20 Kg to less than 40 Kg	❖ 31 mg twice daily	❖ 3.5 mL twice daily
❖ 40 Kg to less than 60 Kg	❖ 44.3mg twice daily	❖ 5 mL twice daily
❖ 60 Kg or more	❖ 53.2 mg twice daily	❖ 6 mL twice daily

- Do not initiate Givinostat in patients with a platelet count less than 150 x 109/L.
- Monitor platelet counts and triglycerides as recommended during treatment to determine if dosage modifications are needed.

Recommended Dosage

Table:-1 Based on patients body weight

DOSAGE MODIFICATIONS:

Dosage Modifications for Adverse Reactions in Patients 6 Years of Age and Older for the Treatment of DMD.

Based on actual body weight .

If the adverse reaction(s) persist after the first dosage modification, proceed to the second dosage modification.

If the adverse reaction(s) persist after the second dosage modification, DUVYZAT should be discontinued .

Table 2 Dosage Modification For Adverse Reactions:

	First Dosage Modification		Second Dosage Modification	
Weight	Dosage (twice daily)	Oral suspension volume(twice daily)	Dosage (twice daily)	Oral suspension volume(twice daily)
10-20kg	17.7mg	2 mL	13.3 mg	1.5 mL
20-40kg	22.2mg	2.5 mL	17.7 mg	2 mL
40-60kg	31mg	3.5 mL	26.6 mg	3 mL
60 kg+	39.9mg	4.5 mL	35.4 mg	4 mL

CLINICAL TRIALS:

Clinical trials are conducted under a range of different conditions, so the adverse reaction rates observed in one trial may not be directly comparable to those in another and may not accurately reflect what happens in real-world use. In trials involving patients with confirmed Duchenne Muscular Dystrophy (DMD), 222 male patients aged 6 years and older were treated with DUVYZAT. Among them, 210 patients were treated for at least 6 months, 187 for at least 12 months, and 105 for at least 24 months. The safety data for DUVYZAT comes from a double-blind, placebo-controlled, 18-month study of 179 ambulant DMD patients aged 6 years or older who were also on concurrent steroid treatment (Study 1). In this study, the dosage was based on patient weight [see Dosage and Administration table 1]. Certain patients were excluded if they had abnormal test results during screening, such as low platelet, white blood cell, or hemoglobin counts, high triglycerides (greater than 300 mg/dL while fasting), or a prolonged QT interval (QTcF> 450 msec, averaged over three consecutive readings taken 5 minutes apart), or if they had any history of conditions that could increase the risk of torsades de pointes (e.g., heart failure, hypokalemia, or a family history of long QT syndrome). A total of 2% of patients discontinued the study due to adverse reactions. Adverse reactions occurring in more than 5% of DUVYZAT-treated patients, and at least 5% more frequently than in the placebo group, are summarized in *Table 3 below*.

Table 3. **Adverse Reactions Reported in >5% of DUVYZAT-Treated Patients and at Least 5% Greater than Placebo in Study 1**

Adverse Reaction	**DUVYZAT**	**Placebo**
	N=118	**N=61**
	%	**%**
Diarrhea	37	20
Abdominal pain	34	25
Thrombocytopenia	33	0
Nausea\ Vomiting	32	18
Hypertriglyceridemia	23	7
Pyrexia	13	8
Myalgia	9	3
Rash	9	2
Arthralgia	8	2
Fatigue	8	0
Constipation	7	2
Decreased appetite	7	0

CLINICAL PHARMACOLOGY:-

Mechanism of action :

Its mode of action is as an inhibitor of histone deacetylase.

Pharmacodynamics:

Muscle fraction as Determined by MR Spectroscopy: In Study 1, magnetic resonance spectroscopy was used to determine the percentage of fat fraction found in the thigh's vastus lateralis muscles.

Patients treated with Duvyzat had a fat fraction of 748%, whereas those who got a placebo saw an increase of 10.89%.

Electrophysiology of the heart:-After giving Grivinostat 265.8 mg to healthy volunteers for five hours, the maximum mean increase in QTc interval was 13.6 ms (upper confidence range: 17.1 ms), which is roughly five times the recommended dosage of 53.2 mg for DMD patients weighing 60 kg or more.

Pharmacokinetics:

Steady State Concentration are achieved within 5-7 days twice daily dosing.

Absorption: No assessment was made of the degree of bioavailability.

Plasma concentrations peak two to three hours after oral treatment. After eating a high-fat standard meal, the impact of food time to maxima concentration (T max) was delayed by two to three hours. Additionally, exposure increased the area under the plasma concentration time curve (AUC) by approximately 40% and the maxima plasma concentration (C max) by approximately 23%.

Distribution: Givinostat has a blood-to-plasma ratio of 1.3 and is roughly 96% bound to plasma proteins in human blood, with a little amount being found in red blood cells.

Elimination: Givinostat's apparent elimination half-life in plasma is roughly six hours.

Metabolism: In vitro research employing human enzymatic preparations and animal metabolism indicates that gibinostat undergoes substantial metabolism, producing a number of metabolites. CYP450 and UGTs are not involved in the main metabolic processes.

Regarding the efficacy of givinostat, four primary metabolites have been found to be inactive in humans and preclinical species. **Excretion:** A mass balance research in rats showed that metabolism is the main factor driving givinostat clearance, followed by the excretion of its metabolites through the kidneys and bile. Givinostat excretion in the urine is quite little in humans, making up less than 3% of the whole dosage.

WARNINGS AND PRECAUTIONS:

Hematological Changes:

Givinostat may result in a drop in platelet counts. That took place over the first two months of treatment. ϖ For the first two months of treatment, check blood counts every two weeks. After that, check them monthly for the first three months, and then every three months after that.

Elevated Triglycerides:

Givinostat may result in triglyceride increases, or levels above 300 mg/dL. It raises the risk of heart disease, heart attacks, and stroke. ϖTriglycerides should be checked at one, three, and six months, and then every six months after that.

ADVERSE REACTION:

While givinostat is being investigated as a potential treatment for Duchenne muscular dystrophy (DMD), clinical trials have reported several adverse effects. It's essential to note that the severity and frequency of these effects may vary depending on the individual, dosage, and treatment duration.

Typical Side Effects:

1. Gastrointestinal problems: stomatitis (mouth irritation), nausea, vomiting, diarrhoea, and abdominal pain

2. Weakness and weariness: Asthenia (lack of energy), muscle weakness, and increased fatigue

3. Infections, including urinary tract infections and upper respiratory tract infections

4. Headache and lightheadedness: recurring headaches and lightheadedness

5. Skin reactions include rashes, itching, and pruritus.

Reduced Frequency of Adverse Effects:

1.**Blood abnormalities**: Anaemia, thrombocytopenia (low platelet count), and neutropenia (low white blood cell count) are examples of blood abnormalities.
2. **Elevations of liver enzymes:** elevated liver enzyme values, including ALT and AST

3. **Muscular damage**: Rhabdomyolysis, a dangerous disorder that results in the breakdown of muscular tissue, is one type of muscle injury.

4.**Neurological consequences:**Tremors, seizures, and other neurological consequences

5. **Cardiovascular effects:**Changes in blood pressure,heart arrhythmias and variations in blood pressure

Severe side effects :

1. **Severe infections:** illnesses that can be fatal, such sepsis

2. Severe muscle damage: Rhabdomyolysis, a severe form of muscle injury that can result in renal failure

3. Severe allergic reactions: One potentially fatal allergic reaction is anaphylaxis.

GIVINOSTAT'S CURRENT STATUS AND FUTURE DIRECTION:

The regulatory approval process for the histone deacetylase inhibitor Givinostat has advanced significantly. Givinostat, also known as Duvyzat, has been approved by the US Food and Drug Administration (FDA) to treat Duchenne muscular dystrophy (DMD) in patients six years of age and older. Givinostat is the first nonsteroidal medication approved to treat all hereditary types of DMD, making this approval a significant milestone.

Givinostat has been approved by the FDA and designated as an orphan medication in the European Union for the treatment of polycythaemia vera and systemic juvenile idiopathic arthritis. Additionally, Italfarmaco's marketing application for givinostat as a therapy for DMD has been approved by the European Medicines Agency (EMA), which could result in EU approval.

In the future, givinostat is being researched for a number of illnesses besides DMD. Numerous phase II clinical studies are presently being conducted for conditions like myelomas and relapsed leukaemias. With a report providing comprehensive insights into its market size, estimates, and developing trends through 2032, market forecasts indicate that givinostat will continue to rise.

CONCLUSION:

A comprehensive strategy is necessary for the management of Duchenne muscular dystrophy, a severe and debilitating genetic condition. There is an urgent need for new potent and focused therapy, even while the available treatments can help delay the progression of the disease and enhance quality of life. Givinostat gives patients with DMD hope for better treatment outcomes because of its distinct mode of action and encouraging clinical trial findings. To meet the unmet needs of individuals with this crippling illness, more research and the creation of novel medicines are essential.

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