

AGAMREE

Category:

Best Biotechnology Product

Company Name:

Catalyst Pharmaceuticals

Product/Solution Name:

AGAMREE

Compound/Tech Name:

vamorolone

Trade Name:

AGAMREE

Corporate Name:

Catalyst Pharmaceuticals, Inc

Date of Approval:

2023-10-23

Indications:

Duchenne Muscular Dystrophy

Therapeutic Areas:

Duchenne Muscular Dystrophy

General Information File Document upload:

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Background information and need for drug / device:

Duchenne Muscular Dystrophy (DMD) is a devastating X-linked genetic disorder affecting approximately 1 in 3,500-5,000 male births worldwide. This rare disease is caused by loss-of-function mutations in the DMD gene that encodes dystrophin, a critical protein in the membrane cytoskeleton of muscle fibers. The absence of functional dystrophin leads to progressive muscle weakness, inflammation, and degeneration of both skeletal and cardiac muscle, ultimately resulting in wheelchair dependence by adolescence, respiratory failure, and premature death typically in the third decade of life.

The pathophysiology of DMD creates a vicious cycle where dystrophin deficiency leads to muscle membrane instability, chronic inflammation, and progressive fibrosis. Without intervention, boys with DMD experience relentless functional decline, losing the ability to walk independently between ages 7-13, developing respiratory insufficiency requiring ventilatory support, and facing life-threatening cardiomyopathy.

For decades, corticosteroids have represented the gold standard of pharmacological care for DMD due to their potent anti-inflammatory effects. Prednisone, prednisolone, and deflazacort effectively stabilize motor function, control inflammatory symptoms, and slow disease progression, delaying loss of ambulation and respiratory failure by several years. These benefits have made corticosteroids indispensable in DMD management, often extending walking ability by 2-5 years and improving overall survival.

However, long-term corticosteroid use causes severe, dose-limiting adverse effects that significantly impact quality of life and create difficult treatment dilemmas for families and clinicians. These side effects include bone fragility and osteoporosis, severe growth suppression, excessive weight gain and metabolic disturbances, immune suppression, and behavioral and psychiatric changes.

These side effects often force difficult treatment decisions: continue corticosteroids and accept serious adverse effects, or discontinue treatment and face accelerated disease progression. Many families cycle on and off corticosteroids, compromising disease control to manage side effects. This therapeutic dilemma has persisted for over three decades, with no alternatives available despite the recognized need.

The medical community has long sought a treatment that could preserve the life-extending benefits of corticosteroids while eliminating or significantly reducing their harmful effects. This represents one of the most significant unmet needs in DMD care, as the current standard of care forces families to choose between disease progression and treatment toxicity.

Background File Document upload:

N/A

History of the development of the solution/product:

Vamorolone (AGAMREE®), developed by ReveraGen BioPharma and Santhera

Pharmaceuticals, and now licensed to Catalyst Pharmaceuticals for North America, represents a significant advancement in the treatment of Duchenne muscular dystrophy (DMD). This first-in-class, dissociative corticosteroid was designed to address the limitations of traditional corticosteroid treatments such as prednisone/prednisolone and deflazacort, which are associated with severe side effects such as bone fragility, growth stunting, and metabolic disturbances.

Vamorolone (AGAMREE) is an oral, selective, corticosteroid with a differentiated pharmacological profile that binds to the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR), like traditional corticosteroids. However, it lacks an 11 β -hydroxyl/carbonyl moiety on the steroidal C ring, a structural modification that alters its receptor interactions and downstream gene regulation. This change also prevents vamorolone from serving as a substrate for 11 β -hydroxysteroid dehydrogenase enzymes, reducing corticosteroid-associated side effects such as bone fragility. By differentially modulating GR and MR activity and maintaining anti-inflammatory efficacy while mitigating toxicity, vamorolone offers a novel mechanism of action that may position it as a safer, more tolerable alternative to standard corticosteroids for children, adolescents, and adults with Duchenne muscular dystrophy (DMD).

Preclinical studies in mdx mouse models of DMD demonstrated that vamorolone reduced muscle inflammation and improved muscle strength with similar or greater efficacy than prednisolone, notably without stunting growth or increasing cardiac fibrosis, unlike prednisolone.

Following promising preclinical data, initial phase 2a dose-finding (NCT02760264; NCT02760277) and 24-month extension (NCT03038399) trials supported vamorolone's efficacy and safety. Patients demonstrated dose-dependent improvements in motor function, particularly in the time to stand from supine (TTSTAND) velocity, a key measure of disease progression. Importantly, a 30-month open-label extension study (NCT03038399) confirmed long-term efficacy and safety, including the absence of growth stunting.

A pivotal phase 2b VISION-DMD trial (NCT03439670) in corticosteroid-naïve boys aged 4-7 years with DMD showed vamorolone to be an effective treatment. This 48-week randomized, double-blind, placebo- and active-controlled study showed that vamorolone significantly improved TTSTAND velocity compared to prednisone and placebo. Significant improvements in TTSTAND velocity were observed as early as 6 weeks. Furthermore, biomarkers of bone formation and turnover, which were markedly reduced by prednisone, were not significantly affected by vamorolone in this trial, highlighting its bone-sparing potential. The trial also highlighted vamorolone's favorable tolerability, with fewer corticosteroid-associated side effects such as Cushingoid features and growth impairment.

Following Catalyst Pharmaceuticals' acquisition of North American commercial rights in July 2023, vamorolone received its first approval in the USA on October 26, 2023, for the treatment of DMD in patients 2 years of age and older. It also received a positive opinion in the EU in October 2023 for patients 4 years of age and older. This approval underscores vamorolone's successful development from preclinical research to a

clinically validated treatment, offering a much-needed alternative for DMD patients.

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:

AGAMREE® (vamorolone) represents a groundbreaking advancement in the treatment of Duchenne muscular dystrophy (DMD), offering a first-in-class approach that addresses the limitations of traditional corticosteroids. Unlike conventional glucocorticoids, vamorolone is a structurally unique corticosteroid with dissociative properties, selectively modulating the glucocorticoid receptor to retain anti-inflammatory efficacy while reducing activation of gene pathways responsible for adverse effects. This unique mechanism allows for effective disease management with a significantly improved safety profile, reducing common steroid-associated side effects such as growth suppression, bone demineralization, and behavioral disturbances. The innovation of AGAMREE lies in its ability to dissociate the beneficial anti-inflammatory actions from the detrimental side effects typically associated with corticosteroid therapy. By preserving muscle function and mitigating inflammation without compromising growth and bone health, AGAMREE addresses a critical unmet need in DMD treatment. Clinical studies have demonstrated that patients treated with vamorolone experience sustained motor function improvements and enhanced quality of life, highlighting its potential to transform the standard of care for DMD. Furthermore, AGAMREE's development sets a precedent for future research into dissociative steroids and their application across various inflammatory and autoimmune conditions. Its innovative design and clinical success underscore the importance of targeted receptor modulation in drug development, paving the way for therapies that offer efficacy without compromising patient safety. As such, AGAMREE not only signifies a significant leap forward in DMD management but also opens new avenues for therapeutic innovation in the broader field of rare and orphan diseases.

Innovation File Document upload:

N/A

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

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IMPORTANT SAFETY INFORMATION

Patients should not take AGAMREE if they are allergic to vamorolone or any of the inactive ingredients in AGAMREE.

What is the most important information I should know about AGAMREE?

- Do not stop AGAMREE, or change the amount taken, without first checking with your healthcare provider. There may be a need for gradual dose reductions to decrease the risk of adrenal insufficiency crisis, which can be fatal.
- There is an increased risk of infection when taking corticosteroids like AGAMREE. Tell your healthcare provider if the patient has had recent or ongoing infections or has recently received a vaccine. Seek immediate medical advice in the case of fever or other signs of infection. Some infections can be severe, and sometimes fatal. Patients should avoid exposure to chickenpox or measles; alert your healthcare provider immediately if exposure occurs.
- Corticosteroids, including AGAMREE, can cause an increase in blood pressure and water retention. Your healthcare provider may monitor for these increases during treatment.
- There is an increased risk of developing a hole in the stomach or intestines in patients with certain gastrointestinal disorders when taking corticosteroids like AGAMREE.
- Corticosteroids, including AGAMREE, can cause severe behavioral and mood changes. Seek medical attention if behavioral or mood changes develop.
- There is a risk of osteoporosis with prolonged use of corticosteroids like AGAMREE, which can lead to vertebral and long bone fractures.
- Corticosteroids like AGAMREE may cause cataracts or glaucoma. Your healthcare provider should monitor for these conditions if AGAMREE treatment continues for more than 6 weeks.
- Immunizations should be up to date according to immunization guidelines prior to starting therapy with AGAMREE. Live-attenuated or live vaccines should be administered at least 4 to 6 weeks prior to starting AGAMREE. Live-attenuated or live vaccines should not be administered in patients taking AGAMREE.
- Rare instances of severe allergic reaction have occurred in patients receiving corticosteroid therapy.

Before taking AGAMREE, tell your healthcare provider about all medical conditions, including if the patient:

- has decreased liver function.
- is pregnant or planning to become pregnant. AGAMREE can harm an unborn baby.
- is breastfeeding or planning to breastfeed. AGAMREE may appear in breastmilk and could affect a nursing child.

Certain medications can cause an interaction with AGAMREE.

Tell your healthcare provider about all the medicines the patient takes, including prescription and over-the-counter medicines, dietary supplements, and herbal products. What are the possible side effects of AGAMREE?

The most common side effects with AGAMREE include facial puffiness (cushingoid features), psychiatric disorders, vomiting, weight gain, and vitamin D deficiency. These are not all the possible side effects of AGAMREE.

Call your doctor for medical advice about side effects.

Please see full Prescribing Information for additional Important Safety Information.

To report SUSPECTED ADVERSE REACTIONS, contact Catalyst Pharmaceuticals, Inc. at 1-844-347-3277 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

References File Document upload:

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