

TEMPLATE
Letter of Medical Necessity
For Medical Procedures Associated with the Administration of AGAMREE (Vamorolone)

Date:

[Insert Name of Medical Director] RE: Patient Name []

[Insurance Company] Policy Number []

[Address] Claim Number []

[City, State, Zip]

Dear [Insurance Company]:

I am writing this letter of medical necessity to provide information related to the treatment of [insert patient name] with AGAMREE (vamorolone), a corticosteroid for the treatment of Duchenne muscular dystrophy in individuals 2 years of age and older. The FDA approval of AGAMREE was based on the data from the pivotal Phase 2b VISION-DMD study. Compared with current standard-of-care corticosteroids, AGAMREE exhibited comparable efficacy, with data suggesting a reduction in adverse events, notably related to bone health, growth trajectory, and behavior.¹

I would like to provide the following information about the potential benefit of AGAMREE in Duchenne patients:

1. Duchenne pathophysiology

Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder characterized by the progressive loss of muscle, primarily in boys. DMD is the result of variants in the dystrophin (*DMD*) gene. It affects one out of 5000 live male births in the US.^{3,4} The average age at diagnosis is approximately five years⁵ but delays in motor milestones (such as sitting, standing independently, climbing, and walking) occur much earlier.⁶

Dystrophin is located beneath the sarcolemma, and functions to connect the subsarcolemmal cytoskeleton to the sarcolemma. A loss of dystrophin in muscle results in inflammation, muscle degeneration, and replacement of muscle with fibroadipose (fat and fibrotic) tissue. The primary symptoms of Duchenne muscular dystrophy are caused by a lack of dystrophin in the muscle. Children with Duchenne lose the ability to walk independently and most become reliant on wheelchairs for mobility by the age of 13.⁸ Most individuals with Duchenne experience serious respiratory, orthopedic, and cardiac complications. By the age of 18, the majority of patients require ventilation support at night.⁹ The average life expectancy is approximately 30 years of age, with respiratory complications and cardiomyopathy being common causes of death.⁹

Standard medical management of Duchenne requires attention to the use of corticosteroids as well as respiratory, cardiac, orthopedic, and rehabilitative interventions aimed at the sequela that progressively worsen throughout the lifespan of Duchenne.⁹ Corticosteroids slow the progression of muscle weakness and delay some of the complications of the disease, but they do not treat or correct the underlying causes of Duchenne.

2. Description of AGAMREE⁷

AGAMREE (vamorolone) is a first-in-class dissociative steroidal anti-inflammatory drug that binds to the same target receptors as the corticosteroid class (glucocorticoid receptor, mineralocorticoid receptor), but shows a distinct chemical structure and differences in mechanism of action. AGAMREE shows less positive gene transcriptional activity (transactivation) than corticosteroids but retains inhibition of nuclear factor κ B proinflammatory pathways (transrepression). AGAMREE uniquely lacks a 11β -hydroxyl/carbonyl moiety on the steroidal C ring, changing structure and activity relationships with the receptors. Further, AGAMREE cannot be acted on by modulatory 11β -hydroxysteroid dehydrogenase enzymes known to be necessary for mediating corticosteroid-associated bone morbidities in mice. Lastly, AGAMREE is a potent antagonist of the mineralocorticoid receptor, whereas most corticosteroids are agonists.⁷

3. Mechanism of action and clinical trial results of AGAMREE²

AGAMREE is a corticosteroid that acts through the glucocorticoid receptor to exert anti-inflammatory and immunosuppressive effects. The precise mechanism by which AGAMREE exerts its effect in patients with DMD is unknown.²

The effectiveness of AGAMREE for the treatment of Duchenne muscular dystrophy (DMD) was evaluated in a multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled, multinational 24-week study (Study 1; NCT03439670). The study randomized 121 male patients with DMD to one of the following treatment groups: AGAMREE 6 mg/kg/day (n=30), AGAMREE 2 mg/kg/day (n=30), prednisone 0.75 mg/kg/day (n=31), or placebo (n=30) for 24 weeks. After 24 weeks, patients on prednisone and placebo received either AGAMREE 6 mg/kg/day (n=29) or AGAMREE 2 mg/kg/day (n=29) for an additional 20 weeks. The study included patients 4 to less than 7 years of age at time of enrollment in the study who were corticosteroid naïve and ambulatory, with a confirmed diagnosis of DMD. At baseline, patients had a mean age of 5.4 years, 83% were Caucasian, 10% were Asian, and 96% were not Hispanic or Latino.

The primary endpoint was the change from baseline to Week 24 in Time to Stand Test (TTSTAND) velocity for AGAMREE 6 mg/kg/day compared to placebo. TTSTAND velocity is a measure of muscle function that measures the time required for the patient to stand to an erect position from a supine position (floor). The key secondary endpoints consisted of change from baseline to Week 24 in TTSTAND velocity (AGAMREE 2 mg/kg/day vs placebo), 6 Minute Walk Test (6MWT) distance (AGAMREE 6 mg/kg/day vs placebo and 2 mg/kg/day vs placebo) and Time to Run/Walk 10 meters (TTRW) velocity (AGAMREE 6 mg/kg/day vs placebo and 2 mg/kg/day vs placebo). The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes and TTRW measures the time that it takes a patient to run or walk 10 meters. The fixed sequential testing process was applied to the key secondary endpoints in the order listed above.

The primary endpoint and key secondary endpoints were met for the AGAMREE 6 mg/kg/day treatment group. The AGAMREE 2 mg/kg/day treatment group was statistically significant vs. placebo for TTSTAND and 6MWT but was not statistically significant vs. placebo for TTRW.

4. Dosing Schedule of AGAMREE ²

The recommended dosage of AGAMREE is 6 mg/kg taken orally once daily preferably with a meal, up to a maximum daily dosage of 300 mg for patients weighing more than 50 kg. Some patients may respond to a dose of 2 mg/kg daily. Doses may be titrated down to 2 mg/kg/day as needed, based on individual tolerability.

5. Rationale for Treatment

Advances in medical management have significantly improved life expectancy and quality of life. The use of corticosteroids has pushed the age at loss of ambulation to around 13 years old, demonstrating delayed decline of lower limb skeletal muscle. I believe AGAMREE supplied to my patient is medically necessary to help preserve muscle, delaying loss of function, and potentially reduce adverse events, notably related to bone health, growth trajectory, and behavior compared to other commercially available steroid options.¹

6. Summary of Patient's History [You should also include]:

- Chart notes, including the patient's most recent weight
- Genetic tests
- Copy of the patient's insurance cards
- FDA Approval Letter
- Prescribing information
- Recent medical articles
- Letters from other specialists treating the patient such as cardiologists, pulmonologists and physical and occupational therapists
- Patient's psychological factors that are relevant to your chosen treatment
- Side effects associated with other steroids trialed
- Information to educate Medical Director or Pharmacy Director who is not familiar with the disease or treatment

7. Patient's prognosis

- Summary of your professional opinion of the patient's likely prognosis without treatment with AGAMREE, including list of adverse events seen with other steroids . If applicable, consider including rationale for maintaining additional therapies with dosing of AGAMREE.

8. Concluding Remarks

Based on the clinical data available to date, it is my medical opinion that initiating treatment of [patient name] with AGAMREE is medically appropriate and necessary and the procedures required for its administration should be a covered and reimbursed service. This letter outlines [patient name's] medical history, prognoses, and the rationale for treatment with AGAMREE.

Please call my office at **[insert telephone number]** if I can provide you with any additional information. I look forward to receiving your timely response and approval of this claim.

Sincerely,

**[Insert Doctor name and
Participating provider number]**

References

- ¹U.S. Food and Drug Administration, NDA 215239 approval letter, October 26th 2023. https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2023/215239Orig1s000ltr.pdf
- ²AGAMREE (DelandistVamoroloe) [package insert]. Silver Spring, MD: U.S. Food & Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215239s000lbl.pdf. Published October 26, 2023.
- ³Mendell JR, Shilling C, Leslie ND, et al. Evidence Based Path to Newborn Screening for Duchenne Muscular Dystrophy. *Ann Neurol* 2012;71:304-313.
- ⁴Mah JK, Korngut L, Dykeman J, Day L, Pringsheim T, Jette N. A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy. *2014;24:482-491*.
- ⁵Ciafaloni E, Fox DJ, Pandya S, Westfield CP, Puzhankara S, Romitti PA, et al. Delayed diagnosis in Duchenne muscular dystrophy: data from the muscular dystrophy surveillance, tracking, and research network (MD-STARnet). *J Pediatr* 2009;155:380-385.
- ⁶Bushby K, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management *Lancet Neurol* 2018
- ⁷Guglieri, Michela, et al. "Efficacy and Safety of Vamorolone vs Placebo and Prednisone among Boys with Duchenne Muscular Dystrophy: A Randomized Clinical Trial." *JAMA Neurology*, vol. 79, no. 10, 29 Aug. 2022,
- ⁸Bello L, Gordish-Dressman H1, Morgenroth LP1, Henricson EK1, Duong T1, Hoffman EP1, Cnaan A1, McDonald CM2; CINRG Investigators. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. *Neurology*. 2015
- ⁹Birnkrant DJ, Bushby K, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management *Lancet Neurol* 2018