PDL DRUG REVIEW

Proprietary Name: Agamree®
Common Name: vamorolone oral suspension
PDL Category: Glucocorticoids

Comparable Products	Preferred Drug List Status
Emflaza	Non-Preferred with Conditions
Prednisone	Preferred

Pharmacology/Usage: Vamorolone, the active ingredient of Agamree®, is a corticosteroid. It acts through the glucocorticoid receptor to exert anti-inflammatory and immunosuppressive effects. The exact mechanism by which vamorolone exerts its effect in patients with Duchenne muscular dystrophy is not known.

Indication: For the treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older.

There is no pregnancy category for this medication; however, the risk summary indicates that Agamree® is indicated for use for the treatment of DMD, which is a disease of young male patients. However, corticosteroids in general should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism. There are no data of use during pregnancy. The safety and efficacy of use in the pediatric population below the age of 2 years have not been established.

Dosage Form: Oral Suspension: 40mg/ml. Orange flavor.

Shake well for about 30 seconds prior to administration. Use only the oral syringe provided with the product. Discard any used suspension remaining after 3 months of first opening the bottle.

Recommended Dosage: Administer all immunizations per immunization guidelines prior to starting Agamree® treatment. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting treatment.

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

Regarding discontinuation, the dosage of Agamree® must be decreased gradually if the drug has been administered for more than one week.

Moderate hepatic impairment increases vamorolone exposure. Reduce the Agamree® dosage in patients with mild to moderate hepatic impairment. The recommended dosage in patients with mild to moderate hepatic impairment is 2mg/kg PO QD preferably with a meal, up to a maximum daily dosage of 100mg for patients weighing more than 50kg. There is no clinical experience of use in patients with severe hepatic impairment, and a dosing recommendation cannot be provided for patients with severe hepatic impairment.

Patients can be switched from oral corticosteroid treatment (such as prednisone or deflazacort) to Agamree® without treatment interruption or period of prior corticosteroid dosage reduction to minimize the risk for adrenal

insufficiency. Patients switching after long-term treatment with oral corticosteroids should start Agamree® at a dosage of 6mg/kg/day.

Drug Interactions: The co-administration of Agamree® with itraconazole, a strong CYP3A4 inhibitor, increases vamorolone exposure. Reduce the dosage of Agamree® in patients when strong CYP3A4 inhibitors are used concomitantly. The recommended dosage of Agamree® when administered with strong CYP3A4 inhibitors is 4mg/kg PO QD preferably with a meal, up to a maximum daily dosage of 200mg for patients weighing more than 50kg. Doses may be titrated down based on individual tolerability. Dosage adjustments are not required when Agamree® is administered concomitantly with moderate or weak CYP3A4 inhibitors.

Administer all immunizations per immunization guidelines prior to starting Agamree®. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting Agamree®. Patients on Agamree® may receive concurrent vaccinations, except for live-attenuated or live vaccines.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Agamree® 2mg/kg/d) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included Cushingoid features (7%), psychiatric disorders (0%), vomiting (10%), weight increased (0%), vitamin D deficiency (7%), cough (7%), headache (4%), diarrhea (0%), increased appetite (0%), and rhinitis (0%).

Listed % incidence for adverse drug reactions= reported % incidence for drug (Agamree® 6mg/kg/d) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo. The most frequently reported adverse events included Cushingoid features (29%), psychiatric disorders (7%), vomiting (7%), weight increased (8%), vitamin D deficiency (11%), cough (4%), headache (4%), diarrhea (4%), increased appetite (4%), and rhinitis (4%).

Corticosteroids, such as Agamree® can cause serious and life-threatening alterations in endocrine function, especially with chronic use. Monitor for Cushing's syndrome, hyperglycemia, and adrenal insufficiency after Agamree® withdrawal. In addition, patients with hypopituitarism, primary adrenal insufficiency or congenital adrenal hyperplasia, altered thyroid function, or pheochromocytoma may be at increased risk for adverse endocrine events.

Corticosteroids, including Agamree®, suppress the immune system and increase the risk of infection with any pathogen, including viral, bacteria, fungal, protozoan, or helminthic pathogens. Monitor for the development of infection and consider Agamree® withdrawal or dosage reduction as needed. Hepatitis B virus reactivation can occur in patients who are hepatitis B carriers treated with immunosuppressive dosages of corticosteroids. Screen patients for hepatitis B infection before starting immunosuppressive treatment with Agamree®. In addition, corticosteroids may exacerbate systemic fungal infections, may activate latent amebiasis, and should be used with care in patients with known or suspected Strongyloides (threadworm) infestation. Varicella and measles can have a serious or even fatal course in non-immune patients taking corticosteroids.

Corticosteroids, including Agamree®, can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium and calcium. Monitor blood pressure and serum potassium levels.

Agamree® should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency. In addition, literature reports suggest an association between use of corticosteroids and left free wall rupture after a recent myocardial infarction; thus, therapy with Agamree® should be used with great caution in these patients.

There is an increased risk of GI perforation with use of corticosteroids in patients with certain GI disorders. Signs of GI perforation may be masked in patients receiving corticosteroids. Avoid Agamree® if there is a probability of impending perforation, abscess, or other pyogenic infections; diverticulitis; fresh intestinal anastomoses; or active or latent peptic ulcer.

Potentially severe psychiatric adverse reactions may occur with systemic corticosteroids, including Agamree®. Symptoms typically emerge within a few days or weeks of starting treatment and may be dose-related.

Corticosteroids, such as Agamree®, decrease bone formation and increase bone resorption both through their effect on calcium regulation and inhibition of osteoblast function. Bone loss can predispose patients to vertebral and long bone fractures. Consider a patient's risk of osteoporosis before starting corticosteroid treatment. Monitor bone mineral density in patients on long-term Agamree® treatment.

Corticosteroids may cause avascular necrosis.

The use of corticosteroids, such as Agamree®, may produce posterior subcapsular cataracts. Corticosteroids may also cause glaucoma with possible damage to the optic nerves, and may increase the risk of secondary ocular infections caused by bacteria, fungi, or viruses. Corticosteroids are not recommended for patients with active ocular herpes simplex. Intraocular pressure may become elevated in some patients taking corticosteroids. If treatment with Agamree® is continued for more than 6 weeks, monitor intraocular pressure.

Long-term use of corticosteroids, including Agamree®, can have negative effects on growth and development in children.

Patients receiving corticosteroids and concomitant therapy with neuromuscular blocking agents or patients with disorders of neuromuscular transmission may be at increased risk of developing acute myopathy.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of treatment may result in clinical improvement of Kaposi's sarcoma.

Observational studies have shown an increased risk of thromboembolism (including venous thromboembolism), especially with higher cumulative doses of corticosteroids. It is not clear if risk differs by daily dose or duration of dose. Use Agamree® with caution in patients who have or may be predisposed to thromboembolic disorders.

Contraindications: In patients with known hypersensitivity to vamorolone or to any of the inactive ingredients of the product.

Manufacturer: Catalyst Pharmaceuticals, Inc.

Analysis: The efficacy of Agamree® for the treatment of DMD was assessed in a multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled study of 24 weeks in duration which included male patients (N=121) with DMD. Treatment groups included Agamree® 6mg/kg/day (N=30), Agamree® 2mg/kg/day (N=30), prednisone 0.75mg/kg/day (N=31) or placebo (N=30) for 24 weeks. After 24 weeks, patients on prednisone and placebo received either Agamree® 6mg/kg/day (N=29) or Agamree® 2mg/kg/day (N=29) for an additional 20 weeks. Note that information regarding the active prednisone comparator was not found in the prescribing information.

The study included males that were 4 to less than 7 years of age at the time of enrollment into 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, while 83% were Caucasian.

The primary endpoint was the change from baseline to week 24 in the Time to Stand Test (TTSTAND) velocity for Agamree® 6mg/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® 2mg/kg/day vs placebo), 6 minute walk test (6MWT) distance (Agamree® 6mg/kg/day vs placebo and 2mg/kg/day vs placebo) and Time to Run/Walk 10 meters (TTRW) velocity (Agamree® 6mg/kg/day vs placebo and 2mg/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® 6mg/kg/day treatment group. The Agamree® 2mg/kg/day treatment group was statistically significant vs placebo for TTSTAND and 6MWT, but was not statistically significant vs placebo for TTRW. Results are presented in the table below, which was adapted from the prescribing information.

	Placebo	Agamree® 2mg/kg/d	Agamree® 6mg/kg/d
TTSTAND velocity (rises/sec) – primary endpoint with 6mg/kg/d dose			
Baseline	0.200	0.184	0.186
Mean change from baseline	-0.012	0.033	0.048
Difference from placebo	N/A	0.045	0.060
p-value	N/A	0.017	0.002
6MWT distance (meters)			
Baseline	355	316	313
Mean change from baseline	-14	27	29
Difference from placebo	NA	40	42
p-value	N/A	0.004	0.002
TTRW velocity (meters/sec)			
Baseline	1.735	1.563	1.600
Mean change from baseline	0.014	0.141	0.258
Difference from placebo	N/A	0.127	0.244
p-value	N/A	0.103	0.002

Place in Therapy: Agamree® is an oral corticosteroid suspension indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older. Administer all immunization per immunization guidelines prior to starting Agamree®. In addition, administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting Agamree®. The efficacy of Agamree® was assessed in a randomized, double-blind, parallel-group, placebo- and active-controlled study, with the primary endpoint being the change from baseline to week 24 in Time to Stand Test (TTSTAND) velocity for Agamree® 6mg/kg/day as compared to placebo. Statistically significant differences in favor of Agamree® 6mg/kg/day were observed as compared to placebo for the primary endpoint, as well as key secondary endpoints of 6MWT distance and TTRW velocity.

Per the full text by Guglieri et al[2], the total count of treatment emergent adverse events was lowest in the placebo group (n=77), highest in the prednisone group (N=121), and intermediate in the vamorolone groups (2mg/kg/d, n=97; 6mg/kg/d, n=91). One subject withdrew from the study that was receiving prednisone owing to an adverse event (personality change). Height percentile declined in those treated with prednisone but not in those treated with vamorolone (6mg/kg/day p=0.02). There was linear growth delay in the prednisone group but not in the vamorolone groups (6mg/kg/day p=0.02). Similar overall gain in body mass index was seen between the active treatments. Regarding efficacy, the relative efficacy of prednisone and vamorolone 6mg/kg per day were similar for all 5 motor outcomes per a post hoc analysis, including TTSTAND, TTCLIMB (time to climb 4 stairs), TTRW, 6MWT, and North Star Ambulatory Assessment (NSAA). However, vamorolone 2mg/kg/day demonstrated similar efficacy as prednisone for TTSTAND, 6MWT, and NSAA, but was less effective than prednisone for TTRW and TTCLIMB. The authors concluded that vamorolone was safe and effective for the treatment of boys with DMD over 24 weeks, and it may be a safer alternative than prednisone.

There is some evidence to suggest that Agamree® may be safer than prednisone when used as treatment for males with DMD in a phase 3 efficacy trial. It is recommended that Agamree® remain non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Agamree [package insert]. Coral Gables, FL: Catalyst Pharmaceuticals, Inc; 2023.
[2] Guglieri M, Clemens PR, Perlman SJ, et al. Efficacy and safety of vamorolone vs placebo and prednisone among boys with Duchenne Muscular Dystrophy: A randomized clinical trial. *JAMA Neurol*. 2022; 79(10): 1005-1014.