Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

New Drug Evaluation: casimersen, injection

Date of Review: August 2021
Generic Name: casimersen

End Date of Literature Search: April 12, 2021
Brand Name (Manufacturer): Amondys 45 (Sarepta Therapeutics, Inc)
Dossier Received: yes

Research Questions:

1. What is the evidence of efficacy (e.g., symptoms improvement, muscle or pulmonary function, quality of life, or disease progression) for casimersen in patients with Duchenne muscular dystrophy (DMD)?
2. What is the safety of casimersen for the treatment of patients with DMD?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would benefit or be harmed from casimersen?

Summary of Prior Reviews and Current Policy

Therapies approved by the United States (US) Food and Drug Administration (FDA) for treatment of DMD (eteplirsen, golodirsen, viltolarsen, and deflazacort) were previously reviewed by the Pharmacy and Therapeutics (P&T) Committee in February 2021. In a previous review evaluated by the P&T Committee, there was insufficient evidence to evaluate differences in efficacy or safety between deflazacort and other corticosteroids for DMD or other conditions.[1,2] Evidence was limited by small sample sizes, high or unclear risk of bias, incomplete outcome reporting, and inadequate data in a population of US patients.[1,2] Current evidence demonstrates no difference in functional outcomes (e.g., distance traveled in 6 minutes) for eteplirsen or golodirsen compared to placebo. Evidence is significantly limited by high risk of bias and small sample sizes. Prior authorization (PA) is currently required for deflazacort and all target therapies for DMD to ensure medically appropriate use (see **Appendix 2**). Prednisone is available without PA.

Conclusions:

- There is no comparative efficacy or safety data for casimersen compared to other treatments for DMD.
- FDA approval was based on the secondary surrogate endpoint of an ongoing, unpublished, placebo-controlled, phase 3 trial of casimersen 30 mg/kg intravenously once weekly. An interim analysis in 43 children with DMD on concomitant chronic corticosteroids demonstrated a slight increase in dystrophin protein levels over 48 weeks with casimersen compared to baseline. Dystrophin levels were evaluated by Western blot and reported as a percent of normal levels. In patients treated with casimersen, dystrophin levels increased from baseline by 0.81% of normal (standard deviation [SD] 0.70) compared to an increase of 0.22% of normal (SD 0.49) in patients treated with placebo (mean difference (MD) of 0.59% between groups; 95% CI not reported; p=0.004).[3] It is not known if improvement in dystrophin correlates to clinical outcomes. There is currently no evidence that use of casimersen has any impact on symptoms, muscle or pulmonary function, quality of life, or disease progression in patients with DMD mutations amenable to exon 45 skipping. The trial is unpublished and risk of bias cannot be fully assessed.

Author: Sarah Servid, PharmD

- There is insufficient evidence to verify long-term safety of casimersen. Evidence is limited by the small population of patients which have been exposed to therapy. At the time of FDA approval, 59 patients had been on therapy for more than 48 weeks and only 19 patients had been on therapy for more than 120 weeks.[3] Patients with markers of severe disease (e.g., patients unable to complete baseline functional tests, with severe pulmonary disease or left ventricular ejection fraction less than 50%) were excluded from clinical trials.[3] Like other targeted therapies for DMD, casimersen labeling includes warnings for renal adverse events, and due to the intravenous route of administration, there is possible risk of serious infections related to use of indwelling catheters, particularly in patients receiving chronic corticosteroids.[4]

Recommendations:

- Update prior authorization (PA) criteria for DMD to include casimersen.

Background:

Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder caused by the absence of a functional dystrophin protein. DMD primarily affects males and is the most common type of muscular dystrophy with an estimated worldwide prevalence of 1.7 to 4.2 in 100,000 patients.[5] In the US, it is estimated that Duchenne and Becker muscular dystrophies may affect 1.4 to 2 in 10,000 males ages 5 to 9 years,[5,6] and the estimated incidence of new DMD patients is 1 in approximately 5000 male births.[7] Patients with DMD experience progressive muscle deterioration leading to loss of ambulation and decreased muscle strength. Long-term complications include respiratory failure, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications can lead to wheelchair dependence by age 12 and death at an early age.[5] In a recent systematic review assessing median survival of patients with DMD, improved trends in survival over time were identified which was attributed to improvements in care, including use of ventilator support, leading to a decrease in respiratory-associated deaths in this population.[8] Age of death in patients in earlier decades (e.g., 1960s-1970s), was significantly earlier than age of death for patients who died in more recent decades.[8] The pooled median survival was 29.9 years (95% CI 26.5 to 30.8) in patients with ventilator support compared to 19 years (95% CI 18 to 20.9) in patients without ventilator support.[8]

There is currently no curative treatment for DMD, and therapy focuses on improving symptoms, enhancing quality of life, and decreasing disease progression. Guidelines from the American Academy of Neurology recommend initiation of corticosteroids, either deflazacort or prednisone, as first-line treatment for ambulatory children with a decline in motor function to delay loss of ambulation, preserve pulmonary function, and reduce risk of scoliosis.[5,9] Corticosteroids are often continued if patients become non-ambulatory, though the continued benefits are less clear with progressive disease.[5] Other non-pharmacological therapies which are often essential in disease management include physical therapy and use of support devices such as braces and wheelchairs.[5] As the disease progresses, mechanical ventilation and spinal surgery may be used to improve pulmonary function and decrease pain from scoliosis and vertebral fractures.[5]

Recent new therapies approved for DMD include targeted, exon-skipping therapies. The theoretical goal of these therapies is to modify mRNA splicing and increase the amount of dystrophin protein in cells, thereby correcting the underlying disease process. Using this mechanism, a truncated dystrophin protein is formed. While preclinical animal studies indicate truncated dystrophin can be functional, the level of function associated with the truncated protein is unknown and may vary depending on the inherited mutation.[10] Targeted therapies are approved for specific mutations that are amenable to exon skipping. Eteplirsen was approved in 2016 for DMD with mutations amenable to exon 51 skipping. Approximately 13% of patients with DMD are thought to have mutations amenable to exon 51 skipping.[11] In 2019 and 2020, golodirsen and viltolarsen were approved for patients with mutations amenable to exon 53 skipping (thought to represent about 8% of the DMD population or approximately 1200 patients in the US).[12] Most recently, casimersen was approved for patients with mutations amenable to exon 45 skipping. All therapies have the same mechanism of action and are administered as weekly intravenous infusions.

These therapies have been approved based on changes in dystrophin protein. While eteplirsen and golodirsen have shown a slight increase in dystrophin (<1% of normal dystrophin levels), the impact of these therapies on clinical outcomes had not been demonstrated in randomized controlled trials.[13,14] In the trial used for eteplirsen approval (n=12), there was no difference observed in the 6-minute walk test (6MWT) at 24 or 48 weeks compared to placebo. While subsequent follow-up studies have evaluated pulmonary, cardiac, and muscle function in this population, they are limited by their single-arm observational design, small sample size, and lack of comparator groups or comparison to historical control.[15-18] Similarly, there are no published, placebo-controlled studies evaluating functional outcomes with golodirsen, and FDA review of available clinical outcomes identified no substantial difference from natural history data.[12] Confirmatory post-marketing, randomized trials have yet to be completed for either therapy.

There is currently no consensus on the minimum change in dystrophin level that may result in a clinical improvement, and available thresholds cited in the literature are currently based on expert opinion. In untreated patients with DMD, documented dystrophin levels typically range from 0 to 0.4% of normal healthy patients.[19] Experts suggests that dystrophin levels less than 3% of normal are typically associated with a phenotype of DMD.[19] Some experts suggest that very minimal improvements in dystrophin level may constitute a beneficial change while others suggest that dystrophin levels at 10-20% of normal would likely correlate to clinically significant changes in muscle symptoms or function.[19,20] In patients with Becker muscular dystrophy, a less severe form of muscular dystrophy, dystrophin protein levels are on average 80% of normal.[19] An FDA analysis evaluating the change in 6MWT per year and dystrophin level changes associated with golodirsen failed to demonstrate a positive correlation (R=0.14), indicating that small increases in a truncated dystrophin protein may not be an adequate surrogate marker for functional improvement.[12]

Clinically important outcomes in DMD include morbidity, mortality, disease progression, motor function, and improvements in motor, pulmonary, or cardiac symptoms. There are multiple methods used assess motor function and strength in patients with DMD including timed functional tests scoring tools. For example, the North Star Ambulatory Assessment (NSAA) is a 17-item scale designed for patients able to ambulate at least 10 meters (total score range 0 to 34).[21,22] It evaluates various functional assessments including standing, hopping, climbing stairs, and rising from the floor. Individual items are rated on a 0 to 2 scale based on ability to perform the test normally (2), able to perform the test with modifications or assistance (1), and inability to perform the test (0). The minimum clinically important difference in NSAA score has not been established. Other standard timed functional tests include time to climb 4 stairs, time to walk 10 meters, time required to stand from a prone position, and the 6MWT which evaluates distance traveled in 6 minutes.[23] In healthy children less than 7 years of age, the distance patients are able to walk is expected to remain stable or improve over time with estimated mean walk distances ranging from 500-700 meters.[18,24,25] The minimum clinically important difference in the 6MWT for patients with DMD is approximately 30 meters.[23] NSAA scores less than 16 are more often correlated with 6MWT of less than 300 meters and scores greater than 30 correlate moderately with 6MWT of more than 400 meters.[22] The NSAA is generally considered a more comprehensive measure of functional status compared to other functional outcomes, but the score is often very dependent on patient effort.[19] Pulmonary function is often evaluated during clinical trials using spirometry. In patients with DMD, current evidence demonstrates a gradual decline in pulmonary function tests beginning around 5 years of age (about 4-7% per year of percent predicted forced vital capacity [FVC] and peak expiratory flow [PEF]).[26,27] However, there is currently only limited data to correlate decline in percent predicted FVC or PEF to clinical outcomes such as need for mechanical ventilation or airway clearance.[26]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Casimersen was approved based on interim results from a single, ongoing, unpublished, double-blind, multicenter, placebo-controlled phase 3 study (NCT02500381).[4] The primary endpoint in the ongoing study is change in the 6MWT from baseline to 96 weeks, but FDA approval was based on changes in dystrophin protein from baseline to 48 weeks, a secondary study endpoint. The study is projected to enroll 111 patients eligible for exon 45 skipping with expected completion in 2023. Forty-three patients had dystrophin results available for interim analysis by the FDA. Eligible patients were 7 to 13 years of age, had mutations amenable to exon 45 skipping, and were on a stable dose of corticosteroids.[3] Patients were required to have be ambulatory with a 6MWT between 300 and 450 meters, have stable pulmonary function with FVC of at least 50% of predicted, and have a left ventricular ejection fraction (LVEF) greater than 50% which limits applicability in patients with progressive or severe disease.[3]

As the study is unpublished, risk of bias cannot be assessed. However, there were documented differences in baseline characteristics between groups including slight differences in dystrophin at baseline, time since diagnosis, and duration of steroid use. Dystrophin level at baseline was 0.93% of normal (SD 1.67) for patients treated with casimersen and 0.54% of normal (SD 0.79) for patients treated with placebo.[3] Patients randomized to placebo also had, on average, a shorter time since diagnosis (by 3 months) and a longer duration of steroid use (by 6 months).[3] Differences in baseline characteristics can increase risk of selection bias and decrease certainty regarding whether the observed results are truly related to a treatment effect. It is currently unclear how these differences may impact study outcomes.

Dystrophin levels were evaluated by Western blot at 48 weeks and were reported as a percent of normal levels. Dystrophin level increased from baseline by 0.81% of normal (SD 0.70) in patients treated with casimersen and by 0.22% of normal (SD 0.49) in patients treated with placebo (MD of 0.59% between groups; 95% CI not reported; p=0.004).[3] Other analyses to evaluate the amount of exon 45 skipping by RT-PCR demonstrated more exon skipping with casimersen therapy and were used to support the primary analysis. Several sensitivity analyses were performed by the FDA and produced results consistent with the primary analysis.[3] Sensitivity analyses excluded several outlier patients with large dystrophin levels at baseline, and evaluated dystrophin levels above and below the lower limit of quantification were.[3]

Similar to other targeted therapies for DMD, the clinical benefit of casimersen has yet to be determined. Currently, there are no data available to evaluate clinical outcomes of functional status, symptom improvement, disease progression, or impact on quality of life. Additionally, it is unclear whether improvements in dystrophin correlate to clinical outcomes, and there is no consensus on what difference in dystrophin may be clinically significant. Though it is difficult to make comparisons between trials due to differences in populations, genotypes, and variability in methods used for evaluation of dystrophin, the small magnitude of dystrophin improvement for casimersen appears to be similar to change in dystrophin observed with other targeted therapies for DMD.[2]

Clinical Safety:
At the time of approval, 76 patients were included in the safety dataset for casimersen. Fifty-nine patients had been on therapy for more than 48 weeks and only 19 patients had been on therapy for more than 120 weeks.[3] The most common adverse events associated with treatment included upper respiratory tract infections, cough, pyrexia, headache, arthralgia and oropharyngeal pain (**Table 1**). Adverse events which occurred in 10% to 20% of the population, and were more commonly reported than placebo, included ear pain, nausea, ear infection, post-traumatic pain, and dizziness.

Table 1. Common Adverse events occurring in more than 20% of treated patients and at least 5% more frequent than placebo[4]

Adverse reaction	**Casimersen (n=27)**	**Placebo (n=16)**
Upper respiratory tract infection	65%	55%
Cough	33%	26%
Pyrexia	33%	23%
Headache	32%	19%
Arthralgia	21%	10%
Oropharyngeal Pain	21%	7%

Serious adverse events occurred in 17 patients (22%), the most common being fractures and rhabdomyolysis.[3] Three serious adverse events associated with presence of an indewelling port were documented in a single patient (bacteremia, septic embolus, and vena cava thrombosis).[3] Rhabdomyolysis occurred in 2 patients (6%) treated with placebo compared to 4 patients (7%) treated with casimersen.[3] Most patients experiencing rhabdomyolysis had identifying triggers known to be associated with rhabdomyolysis in patients with DMD including moderate to vigorous physical exercise and exposure to sevoflurane, a general anesthetic. One patient treated with casimersen experienced rhabdomyolysis and cardiac arrest subsequent to general anesthesia and surgery for a central venous port placement.[3]

Like other oligonucleotides for DMD, casimersen labeling includes warnings for serious renal adverse reactions based on data from non-clinical studies. No serious renal adverse events were observed in clinical studies, though more treatment emergent adverse events suggestive of renal injury occurred with casimersen treatment (including increased urine protein/creatinine ratio [n=1] and proteinuria [n=5]), compared to none in the placebo group.[3] Additionally, more patients treated with casimersen had a positive urine dipstick above 1+ compared to placebo.[3]

Look-alike / Sound-alike Error Risk Potential: None identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Functional or symptom improvement (motor, pulmonary, or cardiovascular)
2) Quality of life
3) Disease progression
4) Mortality
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Efficacy Endpoint:
1) Dystrophin protein production

Table 2. Pharmacology and Pharmacokinetic Properties.[4]

Parameter	
Mechanism of Action	binds to Exon 45 of the dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing and producing an internally truncated dystrophin protein
Oral Bioavailability	N/A (administered intravenously)
Distribution and Protein Binding	8.4% to 31.6% protein binding (not concentration-dependent) Vd = 367 mL/kg at steady state
Elimination	Plasma clearance 180 mL/hr/kg > 90% excreted unchanged in the urine
Half-Life	3.5 hours (SD 0.4)
Metabolism	N/A

Abbreviations: kg= kilograms; L=liters; N/A = not applicable; Vd = volume of distribution; SD = standard deviation

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. NCT02500381 FDA Summary Review[3] Phase 3, DB, PC, MC RCT	1. casimersen 30 mg/kg/ week IV 2. placebo 48 weeks Interim results reported at 48 weeks 96 week double blind treatment phase followed by 48 week open-label phase	Demographics: - Mean age: 9 yrs - White: 86% - Mean (SD) dystrophin 1. 0.93% (SD 1.67) 2. 0.54% (SD 0.79) - Weight ≥median 1. 13 (48%) 2. 9 (56%) - Mean BMI: 1. 19.3 kg/m^2 (SD 4.1) 2. 18.8 kg/ m^2 (SD 4.4) - Months since diagnosis 1. 68 (SD 36) 2. 65 (SD 35) - Months of steroid use: 1. 43 (SD 22) 2. 49 (SD 27) - Corticosteroid: 74% deflazacort - Corticosteroid frequency daily: 86% Key Inclusion Criteria: - Age 7-13 yrs - DMD amenable to exon 45 skipping - Stable steroid dose in prior 6 months - Stable cardiovascular therapy in the prior 12 wks - Mean 6MWT between 300 and 450m - Stable pulmonary function with FVC≥50% predicted Key Exclusion Criteria: - LVEF <50% - Need for nocturnal ventilation - QT_C ≥450 msec - Major surgery or changes to the physical therapy regimen within the prior 3 months - Other clinically significant illness	Interim Analysis 1. 27 2. 16	Primary Endpoint: Change in 6MWT from baseline: NR Secondary Endpoints: Change from Baseline in Dystrophin Protein Levels Determined by Western Blot at 48 weeks 1. 0.81% (SD 0.70) 2. 0.22% (SD 0.49) 1 vs. 2: 0.59%; p=0.004 Other secondary clinical outcomes were not reported including ability to rise independently from the floor, time to loss of ambulation, change in the NSAA from baseline, and change in the forced vital capacity percent predicted from baseline	NA	SAE NR DC due to AE: 0%	NA for all	**Risk of Bias (low/high/unclear)**: FDA approval was based on an interim analysis of a secondary endpoint. Interim results are unpublished and the study is ongoing (with estimated completion date in 2023). Risk of bias cannot be fully assessed. **Applicability**: Patient: Patients were ambulatory and able to complete all baseline functional assessments. Patients with acute illness or cardiomyopathy were excluded limiting applicability in patients with severe disease. All enrolled patients were on stable therapy with a corticosteroid, the current standard of care for DMD. The majority of enrolled patients were white, limiting applicability for other races and ethnicities. Intervention: Weekly doses of 4 mg/kg to 30 mg/kg were evaluated in an early phase I/II trial of 12 participants, but treatment response by dose was not assessed.[28] All enrolled patients were prescribed first-line therapy with corticosteroids; there is limited evidence for efficacy or magnitude of benefit when administered without corticosteroids. Comparator: Placebo appropriate to determine efficacy. Outcomes: The outcome evaluated in this interim analysis is a surrogate marker and it has not yet been correlated with functional outcomes. There is no agreement on what level of dystrophin may result in a clinically important improvement. Setting: This ongoing study is currently recruiting patients in the US, Australia, Canada, multiple European countries, Israel, and Russia.

Abbreviations [alphabetical order]: 6MWT = 6 minute walk test; AE = adverse events; ARR = absolute risk reduction; BMI = body mass index CI = confidence interval; DC = discontinuation; DMD = Duchenne muscular dystrophy; FDA = Food and Drug Administration; LVEF = left ventricular ejection fraction; MC = multicenter; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = non-significant; NSAA = North Star Ambulatory Assessment; RCT = randomized controlled trial; SAE = serious adverse events; SD = standard deviation; wks = weeks; yrs = years

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AMONDYS 45 safely and effectively. See full prescribing information for AMONDYS 45.

AMONDYS 45 (casimersen) injection, for intravenous use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

AMONDYS 45 is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with AMONDYS 45 *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio should be measured before starting AMONDYS 45 (2.1)
- 30 milligrams per kilogram of body weight once weekly (2.2)
- Administer as an intravenous (IV) infusion over 35 to 60 minutes via an in-line 0.2 micron filter (2.2, 2.4)
- Dilution required prior to administration (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/2 mL in a single-dose vial (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Kidney Toxicity: Based on animal data, may cause kidney toxicity. Kidney function should be monitored; creatinine may not be a reliable measure of renal function in DMD patients. (5.1, 13.2)

ADVERSE REACTIONS

The most common adverse reactions (incidence >20% and at least 5% higher than placebo) were upper respiratory tract infection, cough, pyrexia, headache, arthralgia, and oropharyngeal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 2/2021

Drugs for Duchenne Muscular Dystrophy

Goal(s):
- Encourage use of corticosteroids which have demonstrated long-term efficacy.
- Restrict use of targeted oligonucleotides for exon skipping and deflazacort to patients with Duchenne Muscular Dystrophy.
- Limit use of deflazacort to patients with contraindications or serious intolerance to other oral corticosteroids.

Length of Authorization:
- 6 months

Requires PA:
- Targeted therapies for exon skipping (see Table 1; pharmacy or physician administered claims)
- Deflazacort

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA Approved Indications for targeted therapies

Drug	Indication	Examples of amenable mutations (list is not all inclusive)
casimersen (Amondys 45®)	Duchenne muscular dystrophy with mutations amenable to exon 45 skipping	Deletion of exons 44, 46, 46 to 47, 46 to 48, 46 to 49, 46 to 51, 46 to 53, 46 to 55, or 46 to 57
eteplirsen (Exondys 51®)	Duchenne muscular dystrophy with mutations amenable to exon 51 skipping	Deletion of exons 43 to 50; 45 to 50; 47 to 50; 48 to 50; 49 to 50; 50; or 52
golodirsen (Vyondys 53®)	Duchenne muscular dystrophy with mutations amenable to exon 53 skipping	Deletion of exons 42 to 52; 45 to 52; 47 to 52; 48 to 52; 49 to 52; 50 to 52; 52; or 54 to 58
Viltolarsen (Viltepso®)	Duchenne muscular dystrophy with mutations amenable to exon 53 skipping	Deletion of exons 42 to 52; 45 to 52; 47 to 52; 48 to 52; 49 to 52; 50 to 52; 52; or 54 to 58

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is the request for treatment of Duchenne Muscular Dystrophy?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Note: Therapies are not indicated for other forms of muscular dystrophy or other diagnoses.
3. Is the request for deflazacort?	**Yes:** Go to #4	**No:** Go to #7
4. Is the patient ≥ 2 years of age?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the patient received, or have contraindications to, all routine immunizations recommended for their age? Note: Routine vaccinations for patients at least 2 years of age typically include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least 2 doses of measles, mumps, rubella, and varicella.	**Yes:** Go to #6 Document physician attestation of immunization history.	**No:** Pass to RPh. Deny; medical appropriateness.
6. Does the patient have a documented contraindication or intolerance to oral prednisone that is not expected to crossover to deflazacort? Note: deflazacort may be an option for patients with clinically significant weight gain associated with prednisone use.	**Yes:** Approve for up to 12 months. Document contraindication or intolerance reaction.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of prednisone.
7. Is the request for continuation of treatment previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #8

Approval Criteria		
8. Is the request for an FDA-approved indication (Table 1)?	**Yes:** Go to #9 Document genetic testing.	**No:** Pass to RPh, Deny; medical appropriateness.
9. Is the request for golodirsen or viltolarsen?	**Yes:** Go to #10	**No:** Go to #12
10. Is the request for combination treatment with 2 or more targeted therapies (e.g., golodirsen and viltolarsen)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #11
11. Has the provider assessed baseline renal function as recommended in the FDA label? Recommended monitoring includes serum cystatin C, urine dipstick, and urine protein-to-creatinine within the past 3 months	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Has the patient been on a stable dose of corticosteroid for at least 6 months or have documented contraindication to steroids?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.
13. Has baseline functional assessment been evaluated using a validated tool (e.g., the 6-minute walk test, North Star Ambulatory Assessment, etc)?	**Yes:** Document baseline functional assessment and approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for golodirsen or viltolarsen?	**Yes:** Go to #2	**No:** Go to #3
2. Has the provider assessed renal function? Recommended monitoring includes urine dipstick monthly, serum cystatin C every 3 months, and protein-to-creatine ratio every 3 months.	**Yes:** Go to #3	**No:** Pass to RPh, Deny; medical appropriateness.

Renewal Criteria		
3. Has the patient's baseline functional status been maintained at or above baseline level or not declined more than expected given the natural disease progression?	**Yes:** Go to #4 Document functional status and provider attestation.	**No:** Pass to RPh, Deny; medical appropriateness.
4. Is there documentation based on chart notes of any serious adverse events related to treatment (e.g., acute kidney injury, infections, etc.)?	**Yes:** Go to #5	**No:** Approve for up to 6 months
5. Has the adverse event been reported to the FDA Adverse Event Reporting System (FAERS)?	**Yes:** Approve for up to 6 months Document provider attestation	**No:** Pass to RPh, Deny; medical appropriateness.

P&T/DUR Review: *8/21 (SS); 2/21; 6/20; 09/19; 11/17; 07/17*
Implementation: *3/1/21; 7/1/20; 11/1/19; 1/1/18; 9/1/17*