MEDICAL COVERAGE POLICY	
SERVICE:	**Medications for Duchenne Muscular Dystrophy**
Policy Number:	**280**
Effective Date:	**01/01/2025**
Last Review:	**11/11/2024**
Next Review:	**11/11/2025**

Important note: *Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.*

SERVICE: Medications for Duchenne Muscular Dystrophy - casimersen (Amondys 45®), eteplirsen (Exondys 51®), golodirsen (Vyondys 53®), viltolarsen (Viltepso®), and delandistrogene moxeparvovec (Elevidys)

PRIOR AUTHORIZATION: Required

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for details.

For Medicare plans, please refer to appropriate Medicare NCD (National Coverage Determination) or LCD (Local Coverage Determination). Medicare NCD or LCD specific InterQual criteria may be used when available. If there are no applicable NCD or LCD criteria, use the criteria set forth below.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid Provider Procedures Manual | TMHP (TMPPM). Texas Mandate HB154 is applicable for Medicaid plans.

Baylor Scott & White Health Plan (BSWHP) may consider medications for Duchenne Muscular Dystrophy (DMD) medically necessary **when ALL of the following universal criteria are met as well as criteria specific to each drug below:**

Universal Criteria:

1. Diagnosis of DMD supported by documentation from the patient's medical records
2. Prescribed by or in consultation with a physician who specializes in treatment of DMD
3. Genetic testing results provided to confirm diagnosis and to identify the specific type of DMD gene mutation
4. Drug to be dosed according to FDA approved labeling
5. Drug will not be used concomitantly with other exon skipping therapies for DMD
6. Member does not have previous treatment with delandistrogene (Elevydis)

Casimersen (Amondys 45®) specific criteria:

1. Member meets all universal criteria
2. Treatment of casimersen is initiated in member before 14 years of age
3. DMD gene mutation is amenable to exon 45 skipping (see Appendix A)
4. Initial authorization requires additional clinical documentation submitted showing:

a. Member is able to achieve an average distance of at least 300 meters while walking independently (e.g., without side-by-side assist, cane, walker, wheelchair, etc.) over 6 minutes

5. Authorization renewal requires additional clinical documentation submitted showing:
   a. Improvement, stabilization, or a reduction in normal decline as evidenced by remaining ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent) measured within 6 months of request
   b. Manageable or no side effects

Eteplirsen (Exondys 51®) specific criteria:

Eteplirsen (Exondys 51®) for the treatment of Duchenne muscular dystrophy is considered not medically necessary as clinical benefit has not been established.

Golodirsen (Vyondys 53®) specific criteria:

1. Member meets all universal criteria
2. Treatment of golodirsen is initiated in member before 16 years of age
3. DMD gene mutation is amenable to exon 53 skipping (see Appendix C)
4. Initial authorization requires additional clinical documentation submitted showing:
   a. Member is able to achieve an average distance of at least 300 meters while walking independently (e.g., without side-by-side assist, cane, walker, wheelchair, etc.) over 6 minutes
5. Authorization renewal requires additional clinical documentation submitted showing:
   a. Improvement, stabilization, or a reduction in normal decline as evidenced by remaining ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent) measured within 6 months of request
   b. Manageable or no side effects

Viltolarsen (Viltepso®) specific criteria:

1. Member meets all universal criteria
2. Treatment of viltolarsen is initiated in member before 10 years of age
3. DMD gene mutation is amenable to exon 53 skipping (see Appendix C)
4. Initial authorization requires additional clinical documentation submitted showing:
   a. Member is able to walk independently without assistive devices
5. Authorization renewal requires additional clinical documentation submitted showing:
   a. Improvement, stabilization, or a reduction in normal decline as evidenced by remaining ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent) measured within 6 months of request
   b. Manageable or no side effects

Delandistrogene moxeparvovec-rokl (Elevidys) specific criteria:

1. Member meets all universal criteria
2. The member is 4 years of age or older
3. Genetic testing conducted to confirm diagnosis and to identify the specific type of DMD gene mutation
4. Member is ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent)
5. Baseline laboratory testing results provided for liver function, platelets, and troponin-1
6. Member does NOT have any of the following:
   a. DMD gene deletion in exon 8 or exon 9
   b. Anti-AAVrh74 total binding antibody titers ≥ 1:400
   c. Concomitant exon skipping therapies for DMD (e.g. casimersen, eteplirsen, golodirsen, viltolarsen, etc.)
   d. Current infection

Initial authorization duration for casimersen, eteplirsen, golodirsen, and viltolarsen is the shorter of 6 months or requested. Authorization renewal duration is the shorter of 6 months or requested.

Only ONE dose per lifetime is medically necessary for delandistrogene moxeparvovec-rokl.

BSWHP considers repeat administration of delandistrogene moxeparvovec-rokl experimental and investigational because the effectiveness of this strategy has not been established.

BSWHP considers casimersen, eteplirsen, golodirsen, viltolarsen, and delandistrogene moxeparvovec-rokl for the treatment of all other indications to be experimental, investigational, and/or unproven.

All requests will be reviewed by a clinical pharmacist and medical director.

BACKGROUND

Duchenne muscular dystrophy (DMD) is an X-linked, recessive disorder that occurs in about 1 in every 3500 to 5000 males. The first signs or symptoms of DMD are noted at about 2.5 years. DMD occurs as a result of mutation(s) in the gene responsible for producing dystrophin. This results in progressive muscle degeneration, leading to a loss of ambulation and possibly even death in the late teenage years. There is no cure for DMD. Standard treatment options have been focused on alleviation of symptoms and management of complications.

Eteplirsen (Exondys 51®) is an “anti-sense” oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) class. PMOs are analogues that selectively bind to RNA to alter gene expression. In the case of eteplirsen, the PMO binds to exon 51 of the dystrophin pre-messenger RNA causing the exon to be skipped and prevents that part of the code from being read during mRNA processing, thereby partially repairing the mutated reading frame in the mRNA coding sequence. Thus, eteplirsen enables the production of an internally truncated, yet functional, dystrophin protein.

For individuals with confirmed mutation of the Duchenne muscular dystrophy gene, eteplirsen promotes exon 51 skipping as evidenced in one randomized controlled trial (RCT) and its open-labelled follow-up study, and interim data from an ongoing RCT.

Interim results from an ongoing study provided evidence that eteplirsen increased dystrophin levels in skeletal muscle in some patients. However, clinical benefit is yet to be established. Ongoing clinical trials are underway to determine the clinical benefit.

In a pooled analysis, Randeree and Eslick analyzed the results of previous studies to evaluate the safety and efficacy of eteplirsen. The average increase in percentage of dystrophin-positive fibers after treatment with eteplirsen was 24.23% The average rate of decline in distance walked for the six-minute walk test was 65 meters. The authors concluded that whether or not this increase in percentage dystrophin-positive fibers and distance walked was clinically significant was unclear, and there is therefore a need for more clinical trials.

In a review article by Hwang and Yokota, they noted that results with eteplirsen appear promising. However, challenges remain as exon-skipping agents can have deleterious non-specific effects.

At this time, the clinical benefit of eteplirsen for the treatment of DMD has not been established.

Golodirsen (Vyondys 53®) is indicated for the treatment of DMD in patients with a confirmed mutation amenable to exon 53 skipping (8% of DMD population). This is the first treatment for DMD in patients with a confirmed mutation amenable to exon 53 skipping. The approval is based on golodirsen's increase in a surrogate marker, dystrophin production, in skeletal muscle. Similar to eteplirsen, no functional outcome was shown in the clinical trials, thus the FDA condition of requiring a post-marketing confirmatory trial for continued approval of golodirsen also exists for full approval. ESSENCE is Sarepta's placebo-controlled, post-marketing confirmatory trial for golodirsen. It is currently enrolling and expected to be complete by 2024.

The golodirsen new drug application (NDA) was supported by a phase I/II trial (4053-101 study). This first-in-human study assessed the safety, tolerability, pharmacokinetics, and efficacy of weekly intravenous golodirsen versus placebo in 25 boys with confirmed deletions of the DMD gene amenable to skipping exon 53. The study consisted of 2 parts; the first part was a randomized 12-week dose-escalation period to assess pharmacokinetics of 4 golodirsen doses. In part 1 of the trial it was shown that golodirsen was safe, well tolerated, and increased exon 53 skipping in patients with DMD and confirmed genetic mutations eligible for exon 53 skipping. All 25 patients had increased exon 53 skipping and showed a ~16-fold increase over baseline in dystrophin protein expression at week 48, illustrating. It was also shown that golodirsen was also well tolerated in all patients.

Viltolarsen (Viltepso®) has the same indication as golodirsen and is indicated for the treatment of DMD in patients with a confirmed mutation amenable to exon 53 skipping. Like golodirsen, viltolarsen's approval was based on the same surrogate marker of dystrophin production in skeletal muscle and will

require verification and description of clinical benefit in a confirmatory trial. The confirmatory trial, RACER53, has started to enroll and will have results by 2024. Viltolarsen achieved a pharmacological effect in half the time of golodirsen and increased dystrophin levels in 24 weeks compared to golodirsen in 48 weeks.

In a phase 2 study 16 patients were enrolled to test the safety, tolerability, and efficacy of viltolarsen. Patents either received a 40mg/kg dose or 80mg/kg dose administered by weekly intravenous infusion. A significant drug-induced dystrophin production was seen in both viltolarsen doses while also being well tolerated with no treatment emergent adverse events requiring dose reduction, interruption, or discontinuation occurring. In a timed functions tests such as standing from supine, time to walk/run 10m, and 6-minute walk test; all 16 patients showed significant improvement.

There are no head-to-head comparisons between golodirsen and viltolarsen currently.

Casimersen (Amondys 45®) is the first exon skipping therapy indicated to treat DMD patients who have a mutation of the DMD gene that is amenable to exon 45 skipping. The FDA gave accelerated approval to casimersen based on interim efficacy at Week 48 of the Phase 3 ESSENCE trial. ESSENCE is a global, double-blind, randomized, placebo-controlled trial in which 43 patients who had a muscle biopsy at baseline and Week 48 were evaluated for dystrophin level. Patients were males between the ages of 7 and 13 years. The patients who received casimersen showed a statistically greater increase in dystrophin protein levels in skeletal muscle compared to patients on placebo (P = 0.004). There are no published trials evaluating casimersen for the treatment of Duchenne muscular dystrophy (DMD) to date.

Delandistrogene (Elevidys) is the first gene transfer therapy for DMD approved by the FDA. It is a one-time dose indicated for individuals at least 4 years of age who have a confirmed DMD gene mutation. On June 20, 2024, the FDA granted traditional approval for patients who are ambulatory and also granted accelerated approval for patients who are non-ambulatory based on expression of Elevidys micro-dystrophin in the skeletal muscle which is a shortened version of dystrophin normally expressed in muscles. The drug is inserted into the patient's muscle cells via an adeno-associated (AAV) vector (AAVrh74). Pre-existing anti-AAV antibodies may impede transgene expression at desired levels, so delandistrogene is not recommended in patients with elevated anti-AAVrh74 total binding antibody titers ≥ 1:400. Patients with any deletion in exon 8 and/or 9 in the DMD gene are contraindicated to therapy.

The efficacy of delandistrogene was evaluated in two double-blind, placebo-controlled studies and two open-label studies, which enrolled a total of 218 male patients (including those who received placebo) with a confirmed disease-causing mutation in the DMD gene. Primary efficacy outcome measures were expression of micro-dystrophin in skeletal muscle and total score of patients on the North Star Ambulatory Assessment (NSAA) scale. In Study 1 (NCT 03769116), the overall change in NSAA was not statistically significant between delandistrogene and place, but a subgroup analysis of patients age 4-5 showed a numerical advantage for treatment. Study 2 (NCT 04626674) did not show a clear

association between micro-dystrophin expression and clinical outcome in non-ambulatory patients. Study 3 (NCT 05096221) did not show a statistically significant different in NSAA score, but secondary outcomes considered clinically relevant were noted in time to rise from floor, 10-meter walk/run, and time to ascend 4 steps. The most common adverse reactions seen with delandistrogene administration are vomiting (65%), nausea (43%), liver injury (40%), pyrexia (28%), and thrombocytopenia (8%). Warning and precautions include infusion-related reactions, acute serious liver injury, immune-mediated myositis, and myocarditis.

Appendix

Appendix A - Examples of DMD Gene Mutations (Exon Deletions) Amenable to Exon 45 Skipping (not an all-inclusive list)

- Deletion of exon 44
- Deletion of exon 46-47
- Deletion of exon 46-48
- Deletion of exon 46-49
- Deletion of exon 46-51
- Deletion of exon 46-53
- Deletion of exon 46-55

Appendix B - Examples of DMD Gene Mutations (Exon Deletions) Amenable to Exon 51 Skipping (not an all-inclusive list)

- Deletion of exon 50
- Deletion of exon 52
- Deletion of exons 45-50
- Deletion of exons 47-50
- Deletion of exons 48-50
- Deletion of exons 49-50

Appendix C - Examples of DMD Gene Mutations (Exon Deletions) Amenable to Exon 53 Skipping (not an all-inclusive list)

- Deletion of exon 52
- Deletion of exon 45-52
- Deletion of exon 47-52
- Deletion of exon 48-52
- Deletion of exon 49-52
- Deletion of exon 50-52

CODES:

Important note: *Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.*

CPT Codes:	
HCPCS Codes:	J1428 – Injection, eteplirsen (Exondys 51) J1429 – Injection, golodirsen (Vyondys 53) J1427 – Injection, viltolarsen (Viltepso) J1426 – Injection, casimersen (Amondys 45)
ICD10 codes:	G71.0 - Muscular dystrophy [Duchenne muscular dystrophy (DMD)]
ICD10 Not covered:	

POLICY HISTORY:

Status	Date	Action
New	10/22/2020	New policy
Updated	07/22/2021	Added information for casimersen
Updated	10/28/2021	Added coverage criteria, appendices, and updated codes
Reviewed	10/28/2022	No changes
Updated	09/28/2023	Updated Medicaid instructions
Updated	11/11/2024	Updated format and layout to separate out universal criteria, added criteria and background information for delandistrogene, updated authorization duration, added requirement of both RPh and medical director review

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and make modifications based upon the evolution of the published clinical evidence. Should additional scientific studies become available, and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

1. Amondys 45 (casimersen) [prescribing information]. Cambridge, MA: Sarepta Therapeutics, Inc. July 2024.
2. Annals of Neurology, 2018, Vol 84, Issue S22: 2018 Annual Meetings. Abstract 142. Golodirsen Induces Exon Skipping Leading to Sarcolemmal Dystrophin Expression in Patients With Genetic Mutations Amenable to Exon 53 Skipping
3. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. Jan 2010; 9(1):77-93. PMID 19945913
4. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2:

implementation of multidisciplinary care. Lancet Neurol. Feb 2010; 9(2):177-189. PMID 19945914

5. Clemens PR, Rao VK, Connolly AM, Harper AD, Mah JK, Smith EC, McDonald CM, Zaidman CM, Morgenroth LP, Osaki H, Satou Y. Safety, tolerability, and efficacy of viltolarsen in boys with Duchenne muscular dystrophy amenable to exon 53 skipping: A phase 2 randomized clinical trial. JAMA neurology. Aug 2020;77(8):982-91.
6. Confirmatory Study of Eteplirsen in DMD Patients (PROMOVI). Available at: https://www.clinicaltrials.gov.
7. Dhillon S. Viltolarsen: First Approval. Drugs. Jun 2020.
8. Exondys51 (eteplirsen) [prescribing information]. Cambridge, MA: Sarepta Therapeutics, Inc. January 2022.
9. Falzarano MS, Scotton C, Passarelli C, et al. Duchenne muscular dystrophy: from diagnosis to therapy. Molecules. Oct 07 2015; 20(10):18168-18184. PMID 26457695
10. Frank DE, Schnell FJ, Akana C, El-Husayni SH, Desjardins CA, Morgan J, Charleston JS, Sardone V, Domingos J, Dickson G, Straub V. Increased dystrophin production with golodirsen in patients with Duchenne muscular dystrophy. Neurology. May 2020;94(21):e2270-82.
11. Hwang, J., & Yokota, T. (2019). Recent advancements in exon-skipping therapies using antisense oligonucleotides and genome editing for the treatment of various muscular dystrophies. Expert Reviews in Molecular Medicine, 21, E5. doi:10.1017/erm.2019.5
12. Kesselheim AS, Avorn J. Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy. JAMA. Oct 24 2016. PMID 27775756
13. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. Nov 2013;74(5):637-647. PMID 23907995
14. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. Ann Neurol. Feb 2016; 79(2):257-271. PMID 26573217
15. Randeree L, Eslick G. Eteplirsen for paediatric patients with Duchenne muscular dystrophy: A pooled-analysis. J Clin Neuroscience. 2018; 49: 1-6
16. U.S. Food & Drug Administration. FDA News Release - FDA Expands Approval of Gene Therapy for Patients with Duchenne Muscular Dystrophy. June 20, 2024. https://www.fda.gov/news-events/press-announcements/fda-expands-approval-gene-therapy-patients-duchenne-muscular-dystrophy. Accessed September 26, 2024.
17. Viltepso (viltolarsen) [prescribing information]. Paramus, NJ: NS Pharma, Inc. March 2021.
18. Vyondys 53 (golodirsen) [prescribing information]. Cambridge, MA: Sarepta Therapeutics, Inc. June 2024.

***Note**:*
Health Maintenance Organization (HMO) products are offered through Scott and White Health Plan dba Baylor Scott & White Health Plan, and Scott & White Care Plans dba Baylor Scott & White Care Plan. Insured PPO and EPO products are offered through Baylor Scott & White Insurance Company. Scott and White Health Plan dba Baylor Scott & White Health Plan serves as a third-party administrator for self-funded employer-sponsored plans. Baylor Scott & White Care Plan and Baylor Scott & White Insurance Company are wholly owned subsidiaries of Scott and White Health Plan. These companies are referred to collectively in this document as Baylor Scott & White Health Plan.

RightCare STAR Medicaid is offered through Scott and White Health Plan in the Central Texas Medicaid Rural Service Area (MRSA); FirstCare STAR is offered through SHA LLC dba FirstCare Health Plans (FirstCare) in the Lubbock and West MRSAs; and FirstCare CHIP is offered through FirstCare in the Lubbock Service Area.