MEDICAL COVERAGE POLICY	
SERVICE:	**Medications for Duchenne Muscular Dystrophy**
Policy Number:	**280**
Effective Date:	**12/01/2021**
Last Review:	**10/28/2021**
Next Review Date:	**10/28/2022**

Important note:
Unless otherwise indicated, this policy will apply to all lines of business.
Even though this policy may indicate that a particular service or supply may be considered medically necessary and thus covered, this conclusion is not based upon the terms of your particular benefit plan. Each benefit plan contains its own specific provisions for coverage and exclusions. Not all benefits that are determined to be medically necessary will be covered benefits under the terms of your benefit plan. You need to consult the Evidence of Coverage (EOC) or Summary Plan Description (SPD) to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and your plan of benefits, the provisions of your benefits plan will govern. However, applicable state mandates will take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, Federal mandates will apply to all plans. With respect to Medicare-linked plan members, this policy will apply unless there are Medicare policies that provide differing coverage rules, in which case Medicare coverage rules supersede guidelines in this policy. Medicare-linked plan policies will only apply to benefits paid for under Medicare rules, and not to any other health benefit plan benefits. CMS's Coverage Issues Manual can be found on the CMS website. Similarly, for Medicaid-linked plans, the Texas Medicaid Provider Procedures Manual (TMPPM) supersedes coverage guidelines in this policy where applicable.

SERVICE: Casimersen (Amondys 45®), eteplirsen (Exondys 51®), golodirsen (Vyondys 53®), and viltolarsen (Viltepso®) for treatment of Duchenne muscular dystrophy (DMD)

PRIOR AUTHORIZATION: Required

POLICY:

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid TMPPM.

For Medicare plans, please refer to appropriate Medicare coverage policies at CMS.gov (e.g. Local coverage documents and articles, national coverage documents and articles, etc.). If there is no applicable Medicare coverage policy, use the criteria set forth below.

Casimersen (Amondys 45®)

SWHP/FirstCare may consider casimersen (Amondys 45®) medically necessary for the treatment of Duchenne muscular dystrophy (DMD) when ALL of the following criteria are met:

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. Treatment of casimersen is initiated in member before 14 years of age
4. Genetic testing conducted to confirm diagnosis and to identify the specific type of DMD gene mutation AND
    a. DMD gene mutation is amenable to exon 45 skipping (see Appendix A)
5. Casimersen will be dosed according to FDA approved labeling
6. Casimersen will not be used concomitantly with other exon skipping therapies for DMD
7. 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
8. 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®)

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®)

SWHP/FirstCare may consider golodirsen (Vyondys 53®) medically necessary for the treatment of Duchenne muscular dystrophy (DMD) when ALL of the following criteria are met:

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. Treatment of golodirsen is initiated in member before 16 years of age
4. Genetic testing conducted to confirm diagnosis and to identify the specific type of DMD gene mutation AND
    a. DMD gene mutation is amenable to exon 53 skipping (see Appendix C)
5. Golodirsen will be dosed according to FDA approved labeling
6. Golodirsen will not be used concomitantly with other exon skipping therapies for DMD
7. 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
8. 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®)

SWHP/FirstCare may consider viltolarsen (Viltepso®) medically necessary for the treatment of Duchenne muscular dystrophy (DMD) when ALL of the following criteria are met:

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. Treatment of viltolarsen is initiated in member before 10 years of age
4. Genetic testing conducted to confirm diagnosis and to identify the specific type of DMD gene mutation AND
    a. DMD gene mutation is amenable to exon 53 skipping (see Appendix C)
5. Viltolarsen will be dosed according to FDA approved labeling
6. Viltolarsen will not be used concomitantly with other exon skipping therapies for DMD
7. Initial authorization requires additional clinical documentation submitted showing:
    a. Member is able to walk independently without assistive devices
8. 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

Initial authorization duration is the shorter of 6 months or requested.

Authorization renewal duration is the shorter of 12 months or requested.

Casimersen (Amondys 45®), eteplirsen (Exondys 51®), golodirsen (Vyondys 53®), and viltolarsen (Viltepso®) for the treatment of all other indications is considered experimental, investigational, and/or unproven.

OVERVIEW:

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.

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:
CODES: 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:	
ICD10 codes:	G71.0 - Muscular dystrophy [Duchenne muscular dystrophy (DMD)]
HCPCS	J1428 – Injection, eteplirsen (Exondys 51) J1429 – Injection, golodirsen (Vyondys 53) J1427 – Injection, viltolarsen (Viltepso) J1426 – Injection, casimersen (Amondys 45)

CMS:

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

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. The health plan will continue to review clinical evidence related to this policy and may modify it at a later date 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 the health plan 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.

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13. Dhillon S. Viltolarsen: First Approval. Drugs. Jun 2020.
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16. Prescribing Label: Amondys 45 (casimersen). Sarepta Therapeutics Inc; Available at: <http://www.accessdata.fda.gov>. Accessed July 2021.