MEDICAL COVERAGE POLICY	
SERVICE: Golodirsen (Vyondys 53)	
Policy Number:	**259**
Effective Date:	**03/01/2020**
Last Review:	**01/23/2020**
Next Review Date:	**01/23/2021**

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: Golodirsen (Vyondys 53) for treatment of Duchenne muscular dystrophy (DMD)

PRIOR AUTHORIZATION: Not applicable.

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

For Medicare plans, please refer to appropriate Medicare LCD (Local Coverage Determination). If there is no applicable LCD, use the criteria set forth below.

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

Golodirsen (Vyondys 53™) for the treatment of Duchenne muscular dystrophy is considered not medically necessary as a clinical benefit has not been established.

Golodirsen (Vyondys 53™) for the treatment of all other indications is considered experimental, investigational and/or unproven.

OVERVIEW:

On December 12, 2019, the FDA granted accelerated approval to Sarepta's Vyondys 53 (golodirsen), indicated for the treatment of Duchenne muscular dystrophy (DMD). This is the first treatment for DMD in patients with a confirmed mutation amenable to exon 53 skipping. The drug is indicated for the treatment of DMD in patients with a confirmed mutation amenable to exon 53 skipping (8% of DMD population). The approval is based on Vyondys 53's increase in a surrogate marker, dystrophin production, in skeletal muscle. Similar to Exondys 51, no functional outcome was shown in the clinical trials, thus the FDA condition of requiring a post-marketing confirmatory trial for continued approval of Vyondys 53 also exists for full approval. ESSENCE is Sarepta's placebo-controlled, post-marketing confirmatory trial for Vyondys 53. It is currently enrolling and expected to be complete by 2024.

Duchenne muscular dystrophy (DMD) is a neuromuscular X chromosome-linked recessive disease. It is caused by mutations in the dystrophin (DMD) gene that diminish or abolish dystrophin production. Dystrophin is an essential cytoskeletal protein that helps stabilize, strengthen, and protect muscle fibers. Numerous mutations in the DMD gene can cause DMD, including the nonsense mutation, which introduces a premature stop codon within messenger ribonucleic acid (mRNA) and, therefore, prevents

full-length dystrophin production. DMD primarily affects males due to the way the disease is inherited, with a worldwide birth prevalence of approximately 1 in 3500 males.

Patients with DMD experience progressive weakness and wasting of muscle fibers due to a lack of functioning dystrophin. Symptoms usually present before 6 years of age, first affecting the lower limbs and proximal muscles and then the upper limbs and distal muscles. As DMD progresses, normal muscle fibers are replaced by connective tissue and fat. Most patients are wheelchair dependent before 13 years of age. Breathing difficulties and cardiac sequela usually present by 20 years of age. Most patients with DMD die from cardiac or respiratory complications before or during their thirties.

There is no cure for DMD. Standard treatment options have been focused on alleviation of symptoms and management of complications.

The Vyondys 53 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 Vyondys 53 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 Vyondys 53 doses. The second part included a 168-week open-label evaluation of weekly infusions of Vyondys 53 30 mg/kg. Results of the 4053-101 study are unpublished to date, but have been presented at conference proceedings. Investigators reported that treatment with Vyondys 53 significantly improved dystrophin expression in all muscle biopsy samples from baseline to week 48. Clinical efficacy and safety outcomes were not reported. As such, there is insufficient evidence to evaluate the safety and efficacy of Vyondys 53 for the treatment of DMD in patients with confirmed mutation amenable to exon 53 skipping.

There are NO published trials evaluating Vyondys 53 for the treatment of DMD in patients who have genetic mutations amenable to skipping exon 53 of the dystrophin (DMD) gene.

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:	
CPT Not Covered:	
ICD10 codes:	G71.0 - Muscular dystrophy [Duchenne muscular dystrophy (DMD)]
ICD10 Not covered:	

CMS:

POLICY HISTORY:

Status	Date	Action
New	01/23/2020	New policy
	06/29/2020	Logo and language changed to include FC

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. SWHP 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 SWHP 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. 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
Frank D (Cambridge, MA), Mercuri E, Servais L, Straub V, Morgan J, Domingos J, Schnell F, Dickson G, Popplewell L, Seferian A, Monforte M, Guglieri M, Muntoni F
Objective: A 2-part, first-in-human, multicenter study is evaluating the phosphorodiamidate morpholino oligomer (PMO) golodirsen in patients with Duchenne muscular dystrophy (DMD) and genetic mutations amenable to exon 53 skipping. We report key biologic outcomes at baseline and Week 48 of golodirsen treatment.
Methods: Part 1 (completed) was a randomized, double-blind, placebo-controlled, 12-week dose escalation. Part 2 (ongoing) is a 168-week open-label evaluation of once-weekly golodirsen 30 mg/kg. Per protocol, patients had paired muscle biopsies of the biceps brachii at baseline and following 48 weeks of once-weekly treatment with golodirsen. Exon 53 skipping was evaluated using reverse transcription polymerase chain reaction (RT-PCR). A validated Western blot method quantified dystrophin production (primary biological end point). Immunohistochemistry assessed dystrophin localization and sarcolemmal fiber intensity.
Results: Mean percent of normal dystrophin protein significantly increased from 0.095% at baseline to 1.019% at Week 48 (mean change: 0.924%; $P<0.001$). All muscle biopsy samples (N=25) displayed a significant increase from baseline in exon 53 skipping at Week 48 ($P<0.001$). A positive correlation between exon 53 skipping and de novo dystrophin production was observed (Spearman-r=0.500; P=0.011). Mean fiber intensity analysis showed a significant increase from baseline in de novo dystrophin production ($P<0.001$) and confirmed dystrophin sarcolemmal localization.
Conclusions: Golodirsen is the second PMO shown to increase dystrophin expression and facilitate sarcolemmal localization following initiation of exon skipping. These findings further support a role for PMO technology in DMD treatment.