MEDICAL COVERAGE POLICY	
SERVICE: Spinraza (Nusinersen)	
Policy Number:	**230**
Effective Date:	**05/01/2021**
Last Review:	**04/22/2021**
Next Review Date:	**04/22/2022**

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: Spinraza (Nusinersen)

PRIOR AUTHORIZATION: Required.

POLICY:

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

Spinraza (nusinersen) may be medically necessary for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. Determination of coverage will be made after medical review and will be based on the following criteria:

For initiation of treatment:

1. Diagnosis of spinal muscular atrophy type 1, 2, or 3 by a neurologist with expertise in the diagnosis of SMA.
2. Onset of disease before 15 years of age
3. Genetic confirmation of the diagnosis with:
   - 5q SMA homozygous gene deletion or homozygous mutation, OR
   - compound heterozygous mutations
4. Member is NOT dependent on either:
   - Invasive ventilation or tracheostomy, OR
   - Non-invasive ventilation for more than 6 hours per day.
5. Request accompanied by baseline motor ability testing using the Hammersmith Infant Neurological Exam (HINE), the Hammersmith Functional Motor Scale Expanded (HFMSE), the Revised Hammersmith Scale (RHS) for SMA, the Upper Limb Module (ULM), or Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder (CHOP INTEND).
6. Dosing is in accordance with FDA labeling.

For continuation of therapy, all of the following must be met:

- All of above criteria met.
- Request accompanied by assessment of motor ability testing performed within **60 days** of next expected Spinraza (nusinersen) dose administration, using either HINE, HFMSE, RHS,

ULM, or CHOP INTEND, that shows improvement or maintenance of previous improvement. The SAME measurement tool MUST be used for continuation requests as was used for the preceding request:

a. HINE: one of the following: Improvement or maintenance of previous improvement of at least 2 points (or maximum score) increase in ability to kick.
   - ✓ Improvement or maintenance of previous improvement of at least 1-point increase in motor milestones of head control, rolling, sitting, crawling, standing, or walking.
   - ✓ Improvement in more categories of motor milestones than worsening

   OR,
b. HFMSE: improvement or maintenance of previous improvement.
c. RHS: improvement or maintenance of previous improvement.
d. CHOP-INTEND: Improvement or maintenance of previous improvement of at least a 4-point increase in score from pretreatment baseline

For members who have received gene therapy (Zolgensma), Spinraza (nusinersen) may be medically necessary as follows:

To start therapy, member must meet one of the following:

Member recently received gene replacement therapy within the previous 6 months; and member has experienced a declination in clinical status since receipt of gene replacement therapy; OR

Member has previously received gene replacement therapy; and member has experienced a declination in clinical status that represents a potential abatement of gene therapy efficacy;

THEN follow criteria above – "For initiation of treatment"

To continue therapy,

Member has previously received gene replacement therapy; and member has experienced a declination in clinical status that represented a potential failure or abatement of gene therapy efficacy;

THEN follow criteria above – "For continuation of therapy"

ALL requests for Spinraza (nusinersen) will be reviewed by both a clinical pharmacist and a medical director.

This medication will ONLY be authorized for administration by one of the following specialists:

- Board certified neurologist
- Board certified physical medicine and rehabilitation specialist with subspecialty certification in neuromuscular medicine

Spinraza (Nusinersen) is not proven or medically necessary for routine concomitant treatment of SMA in patients who have previously received gene replacement therapy.

SWHP does NOT cover the use of Spinraza (nusinersen) for any other indication, including the following, because it is considered experimental, investigational or unproven (this list is not all-inclusive): Types 0 or 4 SMA

OVERVIEW:

SMA disorders are characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem.

SMA is most often an inherited autosomal recessive disease caused by mutations in chromosome 5q that results in a deficiency in SMN1related proteins. There are four variations of SMA, type I, II, III, and IV which are defined based on the severity of muscle weakness and the age of symptom onset. SMA type I (Werdnig Hoffmann disease) is the most severe. SMA type I affected infants represent about 60% of SMA diagnoses and are symptomatic by 6 months of age. These infants are profoundly hypotonic and often succumb to complications of the disease by their second year of life. Children with SMA type II typically present with symptoms prior to 18 months of age and usually develop the ability to sit but not the ability to stand or walk. Individuals affected by SMA type III, also called Kugelberg Welander disease are generally diagnosed by 18 months but are able to stand and walk. SMA type III affected individuals may live into their thirties and beyond. SMA IV, the least severe, typically presents in the second or third decade of life.

SMN2 is a closely related gene to SMN1 and can compensate for SMN1 deficiency and modify the SMA phenotype. Thus, the phenotype of spinal muscular atrophy (type I, II, III, or IV) is largely related to the number of SMN2 gene copies present.

The incidence of SMA is approximately 4-10 per 100,000 live births with an estimated carrier frequency of 1 in 50. Usual care for SMA is supportive therapy which includes nutrition, physical therapy, and respiratory assistance.

Spinraza® (nusinersen) is a modified antisense oligonucleotide (ASO) designed to treat SMA caused by mutations in chromosome 5q in SMN2 gene. Spinraza increases exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein.

Spinraza was approved by the FDA based on a planned interim efficacy analysis result of a phase III, multicenter, randomized, double-blind, sham-procedure controlled study. There were 121 patients that enrolled in the study. They were randomized 2:1 to receive either Spinraza (n=80) or sham injection (n=41). Inclusion criteria include patients aged 7 months or younger at study entry, who were diagnosed with homozygous gene deletion/mutation or compound heterozygous of 5q SMA gene, 2 copies of SMN2, onset of clinical signs and symptoms consistent with SMA at ≤6 months (180 days) of age, meet requirements of body weight and gestation age.

ENDEAR (Finkel et al., 2017), was a randomized, double-blind, sham-controlled, phase 3 efficacy and safety trial of Spinraza in infants with SMA. Eligible participants had genetic documentation of a homozygous deletion or mutation in the SMN1 gene. They also had two copies of the SMN2 gene, had onset of clinical symptoms that were consistent with SMA at ≤ 6 months of age, were ≤ 7 months of age at screening, and did not have low peripheral oxygen saturation. The primary endpoints were a motor milestone response (defined according to results on the Hammersmith Infant Neurological Examination [HINE]) and event-free survival (time to death or the use of permanent assisted ventilation). For the first primary endpoint, participants were considered to have a motor milestone response if they met the following 2 criteria: improvement in at least 1 category on the HINE (i.e., an increase in the score for head control, rolling, sitting, crawling, standing, or walking of ≥ 1 point, an increase in the score for kicking of ≥ 2 points, or achievement of the maximal score for kicking) and more categories with improvement than categories with worsening. An interim analysis was performed that included 78 participants (51 in the Spinraza group and 27 in the control group) who

had been enrolled for at least 6 months. The analysis showed a benefit–risk assessment in favor of Spinraza; this result prompted early termination of the trial. In the final analysis, 39% of participants in the Spinraza group and 68% in the control group had died or had received permanent assisted ventilation. The median time to death or the use of permanent assisted ventilation was 22.6 weeks in the control group and was not reached in the Spinraza group. The risk of death or the use of permanent assisted ventilation was 47% lower in the Spinraza group than in the control group (hazard ratio, 0.53; 95% CI, 0.32 to 0.89; P=0.005).

Recent studies appear to show that Nusinersen treatment over ~3 years resulted in motor function improvements and disease activity stabilization not observed in natural history cohorts. These results document the long-term benefit of nusinersen in later-onset SMA, including SMA type III.

Classification:

- SMA Type 1 (infantile onset SMA or Werdnig-Hoffmann disease): symptoms are present at birth or by the age of 6 months
- SMA Type 2: onset between the ages of 7 and 18.
- SMA Type 3: onset after 18 months; children can stand and walk independently, although they may require aids.
- SMA Type 4 (adult-onset SMA or Kugelberg-Welander disease): onset in adulthood; are able to walk during their adult years.

MANDATES:

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:	96450 Chemotherapy administration, into central nervous system (CNS) (eg, intrathecal), requiring spinal puncture
CPT Not Covered:	
ICD10 codes:	G12.0 Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann] G12.1 Other inherited spinal muscular atrophy G12.8 Other spinal muscular atrophies and related syndromes G12.9 Spinal muscular atrophy, unspecified
ICD10 Not covered:	
HCPCS Codes	C9489 - Nusinersen 0.1 mg J2326 - Nusinersen (Spinraza)

CMS: LCD L37682 for Nusinersen with effective date 11/21/2019

POLICY HISTORY:

Status	Date	Action
New	03/01/2017	New policy
Update	12/13/2917	Updated code for Spinraza effective 1/1/18
Update	02/13/2018	Coverage reviewed and unchanged.
Update	06/12/2018	Coverage extended to SMA Types 2&3.

Review	08/22/2019	No significant changes.
Review	02/27/2020	Added requirement for using same evaluation tool, testing time window, considerations following gene-replacement therapy.
Review	02/25/2021	No changes
Updated	04/22/2021	Medicaid instructions added

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. Chiriboga CA, Swoboda KJ, Darras BT, et al. Results from a phase 1 study of nusinersen (ISISSMN(Rx)) in children with spinal muscular atrophy. Neurology. 2016; 86(10):890897.
2. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile onset spinal muscular atrophy with nusinersen: a phase 2, open label, dose escalation study. Lancet. 2016; 388: 30173026.
3. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology 2014; 83: 810–817.
4. Mailman M, Heinz J, Papp A, et al. Molecular analysis of spinal muscular atrophy and modification of the phenotype by SMN2. Genetics in Medicine. 2002; 4: 2026.
5. Finkel RS, et. al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med 2017; 377:1723-1732 DOI: 10.1056/NEJMoa1702752
6. Mercuri E, et. al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med 2018;378:625-35.DOI:10.1056/NEJMoa1710504
7. Darras B, Chiriboga C, Iannaccone S, Swoboda K, Montes J, Mignon L, Xia S, Bennett C, Bishop K, Shefner J, Green A, Sun P, Bhan I, Gheuens S, Schneider E, Farwell W, De Vivo D; CS2 and CS12 Study Groups. Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies. Neurology. 2019 May 21;92(21):e2492-e2506. doi: 10.1212/WNL.0000000000007527. Epub 2019 Apr 24. PMID: 31019106
8. Montes J, Dunaway Young S, Mazzone E, Pasternak A, Glanzman A, Finkel R, Darras B, Muntoni F, Mercuri E, De Vivo D, Bishop K, Schneider E, Bennett C, Foster R, Farwell W, CS2 and CS12 Study Groups. Nusinersen improves walking distance and reduces fatigue in later-onset spinal muscular atrophy. Muscle Nerve. 2019 Jul 12. doi: 10.1002/mus.26633 PMID: 31298747