MEDICAL COVERAGE POLICY	
SERVICE: Nusinersen (Spinraza®)	
Policy Number:	**230**
Effective Date:	**12/01/2024**
Last Review:	**09/09/2024**
Next Review Date:	**09/09/2025**

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: Nusinersen (Spinraza®)

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 nusinersen (Spinraza®) medically necessary for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients when ALL of the following criteria are met:

For initiation of treatment:

1. Spinraza (nusinersen) will be administered by one of the following:
   a. Board certified neurologist
   b. Board certified physical medicine and rehabilitation specialist with subspecialty certification in neuromuscular medicine; **AND**
2. Diagnosis of spinal muscular atrophy type 1, 2, or 3 by a neurologist with expertise in the diagnosis of SMA; **AND**
3. Genetic confirmation of the diagnosis with one of the following:
   a. 5q SMA homozygous gene deletion or homozygous mutation
   b. compound heterozygous mutations; **AND**
4. Member is NOT dependent on either of the following:
   a. Invasive ventilation or tracheostomy
   b. Use of non-invasive ventilation beyond naps and nighttime sleep; AND
5. Request accompanied by baseline motor ability testing using one of the following:
   a. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder (CHOP-INTEND)
   b. Hammersmith Functional Motor Scale Expanded (HFMSE)
   c. Hammersmith Infant Neurological Exam Section 2 (HINE-2)
   d. Revised Upper Limb Module (RULM); **AND**
6. Dosing is in accordance with FDA labeling; **AND**
7. Member has not previously failed Spinraza (nusinersen)

For continuation of therapy:

1. All of above criteria met; **AND**
2. Documentation of **ONE** of the following outcome measures within 6 months of the next expected Spinraza (nusinersen) administration. The SAME measurement tool used prior to Spinraza (nusinersen) treatment MUST be used for continuation requests. If re-use of the measurement tool is not appropriate the provider must explain the reason for the change.
   a. CHOP-INTEND (one of the following):
      i. Improvement or maintenance of at least a 4-point increase from pre-Spinraza treatment baseline
      ii. Improvement in more categories of motor milestones than worsening
   b. HFMSE (one of the following):
      i. Improvement or maintenance of at least a 3-point increase from pre-Spinraza treatment baseline
      ii. Improvement in more categories of motor milestones than worsening
   c. HINE-2 (one of the following):
      i. Improvement or maintenance of at least a 2-point (or maximum score) increase in the ability to kick from pre-Spinraza treatment baseline
      ii. Improvement or maintenance of at least a 1-point increase in motor milestones of head control, rolling, sitting, crawling, standing, or walking from pre-Spinraza treatment baseline
      iii. Improvement in more categories of motor milestones than worsening
   d. RULM (one of the following):
      i. Improvement or maintenance of at least a 2-point increase from pre-Spinraza treatment baseline
      ii. Improvement in more categories of motor milestones than worsening

For members who have received gene therapy (i.e. Zolgensma), Spinraza (nusinersen) may be medically necessary when all of the following criteria are met:

1. Member has experienced a declination in clinical status that represented a potential failure or abatement of gene therapy efficacy; **AND**
2. If starting therapy with Spinraza (nusinersen) – Member meets all criteria above under “For initiation of treatment”; **AND**
3. If continuing therapy with Spinraza (nusinersen) – Member meets all criteria above under “For continuation of treatment”

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

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

BSWHP does NOT cover the use of Spinraza (nusinersen) for any other indication (e.g. Type 0 SMA, Type 4 SMA) because it is considered experimental, investigational, and/or unproven.

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 (infantile onset SMA or 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 (intermediate SMA or Dubowitz disease) 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 (juvenile-onset SMA or 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 (late- or adult-onset SMA), the least severe, typically presents in the second or third decade of life. Individuals with SMA type IV SMA can walk during their adult years.

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 SMN1 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.

Maggi et al (2020) showed benefit in HFMSE changes in an independent observational trial focusing on type II and type III patients~~,~~ with the latest onset of disease at 17 years of age in one patient. The trial did not include type IV patients with adult-onset disease. Hagenacker et al (2020) similarly showed benefit in adult age treatment start, but did not specifically target type IV disease. Duong et al (2021) showed continued positive trend in motor function through CHOP-ATEND but not other scales in an observational cohort of patients who were initiated on nusinersen later in life. However, only up to type III patients were included, so ~~its~~ generalizability to type IV patients is limited. While the three aforementioned studies showed benefit in patients initiating treatment into adulthood, a paucity of literature is available examining nusinersen's impact in true type IV or adult-onset disease.

The following age limits for motor function tests have been recommended:

- **CHOP-INTEND (No lower or upper age limit established)**
- **HFMSE (>24 months)**
- **HINE-2 (2-24 months)**
- **RULM (>30 months)**

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)

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
Review	04/21/2022	Medicare instructions added
Updated	04/27/2023	Removed age of onset criteria
Updated	09/28/2023	Updated Medicare and Medicaid instructions
Updated	09/09/2024	Updated layout moving criteria under initiation of treatment (1), updated initiation of treatment language (4b), added criteria under initiation of treatment (7), removed RHS as an acceptable motor function test, extended timeline to 6 months for documentation of motor function, added language to define improvement or maintenance in motor function test, added “improvement in more categories of motor milestones than worsening” to each motor function tests, reworded language to clarify criteria for members who have received prior gene therapy, updated background to include recommended age limits for motor function tests, reformatted background, added references (9-15)

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 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 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. 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
9. Coratti G, et al. Determining Minimal Clinically Important Differences in the Hammersmith Functional Motor Scale Expanded for Untreated Spinal Muscular Atrophy Patients: An International Study. Eur J Neurol. 2024 Apr 24. doi: 10.1111/ene.16309. PMID: 38656662
10. Mazzone ES, et al. Revised Upper Limb Module for Spinal Muscular Atrophy: Development of a New Module. Muscle Nerve. 2016 Oct 4. doi: 10.1002.mus.25430. PMID: 27701745
11. Mercuri E, et al. Nusinersen Versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med. 2018 Feb 14. Doi: 10.1056/NEJMoa1710504. PMID: 29443664
12. Mishra B, et al. “Minimal Clinically Important Difference (MCID) in Patient-Reported Outcome Measures for Neurological Conditions: Review of Concept and Methods.” *Annals of Indian Academy of Neurology*, vol. 26, no. 4, Jan. 2023, pp. 334–43. https://doi.org/10.4103/aian.aian_207_23.
13. Pera M, et al. “Revised Upper Limb Module for Spinal Muscular Atrophy: 12 Month Changes.” *Muscle & Nerve*, vol. 59, no. 4, Feb. 2019, pp. 426–30. https://doi.org/10.1002/mus.26419.
14. Stolte B, et al. “Minimal Clinically Important Differences in Functional Motor Scores in Adults With Spinal Muscular Atrophy.” *European Journal of Neurology*, vol. 27, no. 12, Sept. 2020, pp. 2586–94. https://doi.org/10.1111/ene.14472.
15. Pierzchlewicz K, et al. “Spinal Muscular Atrophy: The Use of Functional Motor Scales in the Era of Disease-Modifying Treatment.” *Child Neurology Open*, vol. 8, Jan. 2021, p. 2329048X2110087. https://doi.org/10.1177/2329048x211008725.

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.