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Policy Number: 035.003

Title: Coverage Determination Policy for Intrathecal Nusinersen (Spinraza)

Regions:	☒ **Texas**	☐ **Florida**	☐ **Indiana**	☒ **New Mexico**

Impacted Areas:

☒ Network Management/Provider Services	☒ Utilization Management
☐ Member services	☐ Case management
☐ Quality Management	☐ Disease management
☐ Credentialing	☒ Claims
☐ IT	☐ Human resources
☐ Administration	☐ Finance
☐ Compliance/delegation	☒ Pharmacy
	☐ ALL

Available LCD/NCD/LCA: None

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Doctors helping patients for more than 25 years

Title: Coverage Determination Policy for Intrathecal Nusinersen (Spinraza)

Table of Contents

Coverage Policy Number: 035.003

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Initial/New Requests

Note: ALL initial Requests will ONLY be approved for 4 loading doses.

A. Spinraza (Nusinersen) is proven and medically necessary for the treatment of **Spinal Muscular Atrophy (SMA)** when patient meets **ALL** of the following criteria are met:

1. Diagnosis of spinal muscular atrophy
2. Submission of medical records (e.g., chart notes, laboratory values) confirming the mutation or deletion of genes in chromosome 5q resulting in **ONE** of the following:
    i. Homozygous gene deletion or mutation (e.g., homozygous deletion of exon 7 at locus 5q13)
    ii. Compound heterozygous mutation (e.g., deletion of SMN1 exon 7[allele 1] and mutation of SMN1 [allele 2])
3. Patient is not dependent on either of the following
    i. Invasive ventilation or tracheostomy
    ii. Use of non-invasive ventilation beyond use for naps and nighttime sleep
4. Submission of medical records (e.g., chart notes, laboratory values) of the baseline exam of at least **ONE** of the following exams (based on patient age and motor ability) to establish baseline motor ability:
    i. Hammersmith Infant Neurological Exam Part 2 (HINE-2) (infant to early childhood)
    ii. Hammersmith Functional Motor Scale Expanded (HFMSE)
    iii. Upper Limb Module (ULM) Test (Non ambulatory)
    iv. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
5. Patient has not previously received gene replacement therapy for the treatment of SMA
6. Patient is not receiving concomitant chronic survival motor neuron (SMN) modifying therapy [e.g., Evrysdi (risdiplam)]
7. Spinraza is being dosed according to FDA Approved Dosing.

Renewal/Continuation of Therapy Requests

B. Spinraza (Nusinersen) is proven and medically necessary for the continuation of treatment for **Spinal Muscular Atrophy (SMA)** when **ALL** of the following criteria are met:
   1. Diagnosis of spinal muscular atrophy
   2. Patient has previously received Spinraza therapy
   3. Patient is not dependent on either of the following
      i. Invasive ventilation or tracheostomy
      ii. Use of non-invasive ventilation beyond use for naps and nighttime sleep
   4. Patient has not previously received gene replacement therapy for the treatment of SMA
   5. Patient is not receiving concomitant chronic survival motor neuron (SMN) modifying therapy [e.g., Evrysdi (risdiplam)]
   6. Submission of medical records (e.g., chart notes, laboratory values) with the most recent results (< 1 month prior to request) documenting a positive clinical response from pretreatment baseline status to Spinraza therapy as demonstrated by at least **ONE** of the following exams
      i. HINE-2 milestones- must meet **ALL** of the following
         1. Must meet **ONE** of the following
            a. Improvement or maintenance of previous improvement of at least two point (or maximal score) increase in ability to kick
            b. Improvement or maintenance of previous improvement of at least one point increase in any other HINE-2 milestone (e.g., head control, rolling, sitting, crawling, etc.), excluding voluntary grasp
         2. Must meet **ONE** of the following
            a. The patient exhibited improvement or maintenance of previous improvement in more HINE motor milestones than worsening, from pretreatment baseline (net positive improvement)
            b. Achieved and maintained any new motor milestones when they would otherwise be unexpected to do so (e.g., sit unassisted, stand, walk
      ii. HFMSE: One of the following
         1. Improvement or maintenance of previous improvement of at least a 3-point increase in score from pretreatment baseline
         2. Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so
      iii. ULM: One of the following

1. Improvement or maintenance of previous improvement of at least a 2-point increase in score from pretreatment baseline
2. Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so

iv. CHOP INTEND: One of the following

1. Improvement or maintenance of previous improvement of at least a 4-point increase in score from pretreatment baseline
2. Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so

7. Spinraza is being dosed according to FDA Approved Dosing.

Spinraza is not proven or medically necessary for ANY of the following:

1) Spinal muscular atrophy without chromosome 5q mutations or deletions
2) Concomitant treatment of SMA in patients who have previously received gene replacement therapy
3) Concomitant treatment of SMA in patients receiving Evrysdi (risdiplam)

FDA Approve Dose and Indication:

Indication	Approved Dosing
Spinal muscular atrophy	• **Loading doses**, 12 mg intrathecally every 14 days for 3 doses; then 12 mg intrathecally 30 days after the third dose (total of 4 loading doses) • **Maintenance**, 12 mg intrathecally every 4 months

General Background:

Spinraza is an antisense oligonucleotide medication for the treatment of SMA. It increases the expression of the survival motor neuron protein by enhancing exon 7 inclusion in survival motor neuron-2 (SMN2) messenger RNA.

Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides.
Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

Spinal muscular atrophy (SMA) is a genetic condition that causes degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem. This results to loss of motor neurons and severe progressive muscular weakness and atrophy. Patients with SMA have deletion/mutation of the survival of motor neuron 1 (SMN1) gene on chromosome 5q13.2. SMA disorders are classified as types 0 through 4 based on degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem

A. **SMA type 0** (prenatal onset of SMA): Patients with this form of SMA usually have one copy of the SMN2 gene. This causes severe weakness and hypotonia. Life expectancy is about 6 months due to respiratory failure.
B. **SMA type 1** (infantile spinal muscular atrophy or Werdnig-Hoffmann disease): Patients with this type have two or three copies of the SMN2 gene. Symptoms of SMA type 1 may include problems moving, swallowing, weak cry, breathing, leg weakness etc.
C. **SMA type 2** (intermediate form; Dubowitz disease): Patients with type 2 SMA have three *SMN2* genes. Weaknesses of the legs are more affected than the arms.
D. **SMA type 3** (juvenile form; Kugelberg-Welander disease): These patients generally have three or four copies of the SMN2 gene. Affected individual may lose the ability to walk due to progressive muscle weakness.
E. **SMA type 4** (late onset): Patients generally have four to eight copies of the SMN2 gene and lifespan is normal.

Motor Assessment Scales Used in SMA[6,7]

1. HINE-2: Hammersmith Infant Neurological Examination Section 2
    i. Used to assess the motor milestones portion of the HINE, includes 8 items: voluntary grasp, ability to kick, head control, rolling, sitting, crawling, standing, and walking
    ii. More suitable for SMA patients who make no or very modest improvements in gaining milestones
    iii. Total HINE score is the sum of points from each item and can range from 0 to 26; with higher scores indicating better function

2. HFMSE: Hammersmith Functional Motor Scale Expanded
    i. Used to investigate a child's ability to perform various activities and is used in later-onset (Type 2 or Type 3) SMA

ii. It consists of 20 items that assess ability to control the head, roll, achieve prop position, kneel, crawl, stand, and take four steps unaided.
iii. The maximum score is 66; a change of 2 to 4 points is considered clinically meaningful

3. ULM: Upper Limb Module Test
   i. Used to investigate the upper limb function of ambulatory and non-ambulatory patients with SMA
   ii. It consists of such items as putting a coin into a cup or elevating a cup to lips, picking a coin, bringing hand to shoulder, lifting weights, opening a zip lock, drawing a line on paper, and other tasks reflecting daily activities; max score is 37.
   iii. It is applicable to both children and adults with SMA (ages 2 to 52 years old)
   iv. ULM is an assessment tool for weaker, nonambulatory individuals with SMA, while the RULM is a revised version of the ULM that covers stronger, ambulatory individuals

4. CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neurological Disorders
   i. Used specifically for evaluating motor function in infants with SMA
   ii. Addresses spontaneous movements, handgrip, head stabilization, flexion and extension of the limbs; scores range from 0 to 64.
   iii. Intended for both infants and older people with an infant's repertoire of motor skills

Clinical Evidence:

Mercuri E. et al conducted a multicenter, double-blind, sham-controlled, phase III trial to evaluate the clinical efficacy, safety, tolerability and pharmacokinetics of nusinersen. The study enrolled 126 children in 24 sites across 10 countries. Major inclusion eligibility criteria were based on documentation of 5q SMA (a homozygous deletion, mutation, or compound heterozygote in *SMN1*) with symptom onset after 6 months. The patients were randomized in a 2:1 ratio to receive 12 mg nusinersen intrathecally (nusinersen group) or a sham procedure (control group) on days 1, 29, 85, and 274. The primary end point was the change from baseline in the Hammersmith Functional Motor Scale–Expanded (HFMSE) score at 15 months of treatment. The scores range from 0 to 66, with higher scores indicating better motor function. Secondary end points measured percentage of patients with a baseline increase of HFMSE score of (≥3 points). The study reporter 5.9 point difference in HFMSE scores favoring nusinersen; (95% confidence interval, $P < 0.001$). Secondary end points results indicated 57% of the nusinersen group had 3 points increase from baseline compared to 26% in the control group ($p < 0.001$). It was concluded that children treated with nusinersen had significant clinical improvement in motor functions as compare with those in the control group.

2020 European Neuromuscular Expert Ad-Hoc Consensus Statement on Gene Replacement Therapy for Spinal Muscular Atrophy:[5]
A group of 13 European neuromuscular experts, conveyed to help aid the rational use of Zolgensma. The group stated with a 100% consensus that "Until now there is no published evidence that combination of two disease modifying therapies (e.g., gene therapy and nusinersen) is superior to any single treatment alone."

Rationale: "SMN1 gene therapy and splicing modifiers for SMN2 both exert their action through an increase of SMN protein. Head to head studies comparing the amount of SMN protein expression or clinical effect size are not available. The combination of both approaches has also not been studied systematically and warrants further investigation. However, from a theoretical point of view one would not expect an additive effect due to the common downstream pathway and mode of action, unless the bio distribution of the different therapeutic compounds was substantially different. Before more evidence is available, combination of both approved therapies should not be part of routine care. In severe symptomatic patients, irreversible degeneration of motor neurons and muscle tissue are probably the most important factors for any lack of efficacy or rescue of the phenotype regardless of the (higher) amount of SMN protein available from any treatment."

HCPCS Code:

HCPCS Code:	Description:
J2326	**Nusinersen (Spinraza)**

Acronyms:

Spinal muscular atrophy (SMA), Survival of motor neuron 1 (SMN1), Hammersmith Infant Neurological Exam (HINE), Hammersmith Functional Motor Scale Expanded (HFMSE), Upper Limb Module (ULM), 6-minute walk test (6MWT), Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), National Coverage Determination (NCD), Local Coverage Determinations (LCD), Food and Drug Administration (FDA)

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