Drug and Biologic Coverage Policy

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Coverage Policy Number 1707

Nusinersen

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Related Coverage Resources

Genetic Testing for Hereditary and Multifactorial Conditions
Onasemnogene Abeparvovec-xioi, Zolgensma
Risdiplam

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Nusinersen (Spinraza™) is considered medically necessary when ALL of the following criteria are met:

- Documented diagnosis of Type 1, 2, or 3 spinal muscular atrophy (SMA) supported by clinical records
- Onset of clinical signs and symptoms consistent with SMA at age 15 years or younger
- Genetic documentation of SMN1 or 5q SMA homozygous or compound heterozygous pathogenic or likely pathogenic gene variants
- The individual does not require permanent ventilation (defined as tracheostomy or ventilatory support for at least 16 hours per day for more than 21 continuous days in the absence of an acute reversible event)
- Established baseline motor ability, documented by the submission of medical records from ONE of the following exams:
    - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
    - Hammersmith Infant Neurological Exam Part 2 (HINE-2)
    - Hammersmith Functional Motor Scale Expanded (HFMSE)
    - Revised Upper Limb Module (RULM) Test
    - 6-Minute Walk Test (6MWT)
- For individuals who have received prior treatment with Evrysdi® (risdiplam oral solution), the health care professional attests that further therapy with Evrysdi will be discontinued

- Individual has not received Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past

Initial authorization is up to 6 months.

Nusinersen (Spinraza) is considered medically necessary for continued use when ALL the following are met:

- Documented diagnosis of Type 1, 2, or 3 SMA supported by clinical records
- Onset of clinical signs and symptoms consistent with SMA at age 15 years or younger
- Genetic documentation of SMN1 or 5q SMA homozygous or compound heterozygous pathogenic or likely pathogenic gene variants
- The individual does not require permanent ventilation (defined as tracheostomy or ventilatory support for at least 16 hours per day for more than 21 continuous days in the absence of an acute reversible event)
- Submission of medical records, documenting a positive clinical response (for example: improvement or stabilization) from pretreatment baseline status with nusinersen (Spinraza) therapy, from ONE of the following exams:
    - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
    - Hammersmith Infant Neurological Exam Part 2 (HINE-2)
    - Hammersmith Functional Motor Scale Expanded (HFMSE)
    - Revised Upper Limb Module (RULM) Test
    - 6-Minute Walk Test (6MWT)
- No concurrent use with Evrysdi®
- Individual has not received Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion)

Reauthorization is up to 12 months.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Nusinersen (Spinraza) is considered experimental, investigational or unproven for ANY other use including the following:

1. Individual was previously been treated with Zolgensma (onasemnogene abeparvovec-xioi)
2. Types 0 or 4 SMA
3. Individual has Complete Paralysis of All Limbs
4. Individual has Permanent Ventilator Dependence

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

Documentation: When documentation is required, the prescriber must provide written documentation supporting the trials of these other agents. Documentation may include, but is not limited to, chart notes, prescription claims records, and/or prescription receipts.

FDA Approved Indications

FDA Approved Indication

Spinraza is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

Recommended Dosing

FDA Recommended Dosing

Spinraza is administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.

Recommended Dosage
The recommended dosage is 12 mg (5 mL) per administration.

Initiate Spinraza treatment with 4 loading doses. The first three loading doses should be administered at 14-day intervals. The 4th loading dose should be administered 30 days after the 3rd dose. A maintenance dose should be administered once every 4 months thereafter.

Missed Dose
If a loading dose is delayed or missed, administer Spinraza as soon as possible, with at least 14-days between doses and continue dosing as prescribed. If a maintenance dose is delayed or missed, administer Spinraza as soon as possible and continue dosing every 4 months.

Drug Availability
Spinraza injection is a sterile, clear and colorless solution supplied as a 12 mg/5 mL (2.4 mg/mL) solution in a single-dose glass vial free of preservatives.

General Background

Disease Overview
Spinal muscular atrophy is a hereditary neuromuscular disorder affecting 8 to 15 in 100,000 live births. (Darras, 2015; Sarnat, 2016) Symptom onset typically occurs in infancy or childhood, and the disease is characterized by progressive muscle weakness ultimately resulting in respiratory failure and death in severe cases. (Tisdale, 2015) Spinal muscular atrophy is classified into 1 of 5 categories (i.e., Type 0 through Type 4) based mainly on age at symptom onset and severity of symptoms, which are widely variable. (Arnold, 2015; Darras, 2015; Tisdale, 2015) Type 1 SMA is the most common form, occurs in infancy, and patients typically do not survive past 2 years of age without respiratory support. Type 4 SMA is the mildest form, characterized by mild proximal muscle weakness starting in adulthood, and does not reduce life expectancy. Patients with clinical symptoms suggestive of SMA undergo genetic testing to confirm the diagnosis. (Arnold, 2015; Darras, 2015; Tisdale, 2015) Table 1 summarizes the characteristics of each type of SMA.

Table 1. Types of Spinal Muscular Atrophy[a]

SMA Type (Proportion)	Age at Onset	Clinical Presentation	Typical Number of *SMN2* Copies	Life Expectancy[b]
Type 0 (< 1%)	Prenatal to birth	• Areflexia • Atrial septal defect • Facial diplegia • Hyopotonia • Joint contracture • Poor feeding • Reduced fetal movement • Respiratory failure (often at birth) • Severe weakness • Weak cry	1 copy	< 6 mo
Type 1 Werdnig-Hoffman disease (25% to 60%)	Birth to 6 mo	• Never able to sit unassisted • Areflexia or hyporeflexia • Dysphagia • Hypotonia • Intercostal muscle weakness • Joint contractures • Lack of head control • Muscle atrophy	2 to 3 copies	< 2 y

SMA Type (Proportion)	Age at Onset	Clinical Presentation	Typical Number of *SMN2* Copies	Life Expectancy[b]
		• Progressive muscle weakness • Poor feeding • Respiratory distress in first year of life • Tongue fasciculations and weakness • Weak cry		
Type 2 Dobowitz disease (20% to 50%)	6 to 18 mo	• Able to sit unassisted • Never able to stand or walk unassisted • Areflexia or hyporeflexia • Aspiration and respiratory distress • Dysphagia • Hypotonia • Intercostal muscle weakness • Joint contractures • Progressive muscle weakness • Scoliosis • Restrictive lung disease • Tremor (minipolymyoclonus) • Tongue fasciculations and atrophy	3 copies	School age to young adult
Type 3 Kugelberg-Welander disease (12% to 30%)	18 mo to adulthood	• Able to walk unassisted, but may eventually require wheelchair • Fasiculations • Muscle hypertrophy (not atrophy) • Progressive proximal weakness • Respiratory muscle weakness is minimal • Severe scoliosis not likely • Tremor (minipolymyoclonus)	3 to 4 copies	Normal
Type 4 (< 5%)	> 21 y	• Able to reach all motor milestones • Mild proximal muscle weakness • Initial symptoms similar to Type 3, but later onset and less severe	≥ 4 copies	Normal

[a] Data derived from Arnold, 2015; Darras, 2015; Kolb, 2015; Sarnat, 2016; and Tisdale, 2015.
[b] Without respiratory support
Abbreviations: SMA = spinal muscular atrophy; SMN = survival motor neuron

- **Genetic Testing**

Most forms of SMA are due to an autosomal recessive homozygous mutation or deletion at the 5q13 position of the survival motor neuron 1 gene (SMN1). (Kolb, 2015) Approximately 1 in 50 people are carriers for the abnormal SMN1 gene. (Arnold, 2015; Tisdale, 2015) The SMN1 gene produces SMN protein which is required for RNA splicing and is present in cells throughout the human body. (Arnold, 2015) Motor neurons normally have higher expression of SMN protein than other cells and are thought to require more SMN in order to function normally. (Arnold, 2015) Patients with SMA are unable to produce adequate levels of SMN protein, resulting in motor neuron degeneration and progressive muscle weakness and atrophy. (Arnold, 2015; Darras, 2015; Tisdale, 2015) The SMN2 gene has an identical amino acid sequence to SMN1 other than a C to T transition in exon 7, and is not affected in patients with SMA. The C to T transition results in exon 7 being spliced out of mRNA transcription from SMN2, and formation of mostly truncated and unstable SMN protein. The SMN2 gene produces a small amount of functional SMN protein. The number of copies of the SMN2 gene is variable in

humans. In SMA, a higher number of SMN2 copies is correlated with less severe disease. (Arnold, 2015; Darras, 2015; Tisdale, 2015)

Pharmacology

Nusinersen is an antisense oligonucleotide that increases the amount of functional SMN protein produced by the SMN2 gene. Nusinersen binds to the ISS-N1 intron to suppress splicing of exon 7 in SMN2. Increased inclusion of exon 7 in SMN2 mRNA transcripts increases production of functional SMN protein. (Rigo, 2014)

Professional Societies/Organizations

Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group is comprised of clinicians and geneticists with expertise in spinal muscular atrophy who developed a treatment algorithm in 2018 for infants who have positive results from a newborn screening test for spinal muscular atrophy. Spinal muscular atrophy Types 1 and 2 comprise a large majority of spinal muscular atrophy cases and account for the majority of patients who screen positively for spinal muscular atrophy and have three or fewer SMN2 gene copies. The Working Group unanimously recommends immediate treatment for these patients to achieve a maximal response to treatment. The NURTURE trial with Spinraza that involved presymptomatic infants who had either two or three SMN2 gene copies supports this recommendation. Treatment recommendations for patients who screen positive for spinal muscular atrophy and have only one SMN2 gene copy or four or more SMN2 gene copies is more complicated. It is likely that patients with only one SMN2 gene copy will likely by symptomatic at birth and the physician should determine if treatment is warranted. The Committee reached consensus that patients with more than four SMN2 copies should not be treated immediately but screened carefully for symptom presentation. (Glascock, 2018)

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

No recommendations are available for nusinersen (Spinraza).

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)

There are no CMS National Coverage Determinations for nusinersen (Spinraza)

Clinical Efficacy

Several different scales were used to assess motor function and efficacy of nusinersen in clinical trials and are summarized in Table 2.

Table 2. Outcomes Used in Clinical Trials Evaluating Nusinersen Efficacy for SMA

Outcome	Description
Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) (Glanzman, 2010)	• Clinician-administered tool designed to evaluate motor function in infants with SMA • Includes 16 items • Total scores range from 0 to 64 points • Higher scores indicate better function
Hammersmith Infant Neurological Exam Section 2 (HINE-2) (De Sanctis, 2016)	• Clinician-administered tool to evaluate motor function in children age 2 to 24 mo • Measures achievement of 26 motor milestones in 8 areas (i.e., walking, standing, crawling, rolling, kicking, grasping, sitting, and head control) • Higher scores indicate better function
Hammersmith Functional Motor Scale-Expanded (HFMSE) Test	• Clinician-administered tool designed to measure motor function in children with SMA Type 2 and 3, including ambulatory SMA Type 3 patients • Includes 33 items, each scored from 0 (unable to perform activity) to 2 (able to perform activity without assistance or modification) • Total scores range from 0 to 66 points • Higher scores indicate better function • 3-point change is considered clinically significant

Revised Upper Limb Module (RULM) Test (Mazzone, 2017)	• Clinician-administered tool designed to evaluate the upper limb function of ambulatory and nonambulatory patients with SMA • Includes 19 items • Total scores range from 0 to 64 points • Higher scores indicate better function • An objective evaluation of functional exercise capability in ambulatory patients
6-Minute Walk Test (6MWT) (Dunaway, 2016)	• An objective evaluation of functional exercise capability in ambulatory patients with later-onset (Type 2 or Type 3) SMA. • Patient walks as far as possible in six minutes

The ENDEAR study randomized 121 infants with SMA to nusinersen 12 mg IT or a sham IT procedure. (Finkel, 2017b) Infants were eligible if they had genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote; onset of clinical signs and symptoms consistent with SMA at 6 months of age or younger; and SMN2 copy number equaled 2. (Finkel, 2017b) An interim efficacy analysis was conducted with a data cutoff date of June 15, 2016 in patients who completed their visit in study day 183. The primary outcomes were time to death or permanent ventilation (evaluated in intention-to-treat set), and the proportion of motor milestone responders (evaluated in the interim analysis set). Permanent ventilation was defined as either receipt of a tracheostomy, or ventilatory support required for 16 or more hours per day for 21 or more days in a row. Motor milestone responders were defined as those who had more HINE-2 category scores that were improved from baseline than worsened, and achieved either an increase of 2 or more points or the maximum HINE-2 score for ability to kick, or an increase of 1 or more points in the HINE-2 score for walking, standing, crawling, sitting, rolling, or head control. Patients who died or withdrew from the study were counted as nonresponders. More patients in the nusinersen group were considered motor milestone responders (41%) compared with sham IT procedure (0%, $P < 0.0001$). Results were consistent across individual HINE-2 category scores and in sensitivity analyses that used slightly different response definitions and methods for accounting for missing data. A majority of the trial participants requiring permanent assisted ventilation saw no improvement in their HINE-2 scores. The time to death or permanent ventilation was not reported. (Finkel, 2017b) Nusinersen IT injection was well-tolerated, and no treatment-related adverse events occurred. (Kuntz, 2016)

The CHERISH study randomized 126 children with SMA to nusinersen 12 mg IT or a sham IT procedure. Individuals were eligible if they had genetic documentation of 5q SMA (a homozygous deletion, mutation, or compound heterozygote in SMN1) with the onset of symptoms after 6 months of age. Eligible participants were also required to demonstrate the presence of the following features at screening: an age of 2 to 12 years, the ability to sit independently, no history of the ability to walk independently (defined as the ability to walk ≥15 ft unaided), and a Hammersmith Functional Motor Scale–Expanded (HFMSE) score of 10 to 54. HFMSE scores range from 0 to 66, with higher scores indicating better motor function. The primary end point was the least-squares mean change from baseline in the Hammersmith Functional Motor Scale-Expanded (HFMSE) score at 15 months of treatment. Secondary end points included the percentage of children with a clinically meaningful increase from baseline in the HFMSE score (≥3 points), an outcome that indicates improvement in at least two motor skills. In the prespecified interim analysis, there was a least-squares mean increase from baseline to month 15 in the HFMSE score in the nusinersen group (by 4.0 points) and a least-squares mean decrease in the control group (by –1.9 points), which prompted an early termination of the trial. In the final analysis, 57% of the children in the nusinersen group as compared with 26% in the control group had an increase from baseline to month 15 in the HFMSE score of at least 3 points. (Mercuri, 2018)

An open-label, sequential-dosing study in 20 infants with SMA symptom onset between 3 and 22 weeks of age was conducted. Motor function and ventilator-free survival in nusinersen-treated patients were compared with historical controls. All patients were between 5 and 30 weeks of age at the time of study enrollment and had homozygous SMN1 deletion or mutation. Most patients (85%) had 2 SMN2 copies, 10% had 3 SMN2 copies, and the number of SMN2 copies was unknown in 1 patient. Nusinersen was administered by IT injection on study days 1, 15, 85, 253, and every 4 months thereafter. The first 4 patients enrolled in the study received nusinersen 6 mg for the first 3 doses and received 12 mg thereafter. The remaining 16 patients received nusinersen 12 mg throughout the study. An interim efficacy analysis was conducted approximately 18 months after the final patient was enrolled in 19 patients who received 2 or more nusinersen doses and completed the

efficacy assessment on day 92. One patient with 3 SMN2 copies, who had a baseline CHOP-INTEND score of 64 points (i.e., maximum score), was excluded from the CHOP-INTEND analysis. The mean change in the CHOP-INTEND score was +11.5 points (P = 0.008 vs. baseline). The CHOP-INTEND score is expected to decrease in SMA Type 1 patients based on a natural history study that showed a decline of 1.27 points per year. Thirteen patients in the nusinersen 12 mg group had 2 SMN2 copies, and 7 achieved a CHOP-INTEND score of greater than 40 points, a score that is rarely achieved in this population. Seven patients died or required permanent ventilatory support, including 2/4 in the nusinersen 6 mg/12 mg group and 5/16 in the nusinersen 12 mg group. The median age of death or permanent ventilation was not reached at the time of the interim analysis. The probability of survival without permanent ventilation was greater in nusinersen-treated patients with 2 SMN2 copies versus historical controls (log-rank test, P = 0.0014) but details of this analysis were unclear. An autopsy was conducted in 3 patients, and more SMN2 transcripts obtained from thoracic spinal cord tissue contained exon 7 (50% to 69%) compared with 15% to 26% in untreated controls. All patients experienced at least 1 adverse event, but most were mild or moderate and consistent with adverse events expected in infants with SMA. No clinically significant changes related to laboratory parameters, neurologic exam, or vital signs occurred. (Finkel, 2017a)

The FDA product label refers to open-label, uncontrolled trials demonstrating benefit in some individuals who had or were likely to develop Type 1, 2, or 3 SMA (symptomatic individuals who were 30 days to 15 years old at the time of their first dose and pre-symptomatic individuals who were 8-42 days at the time of their first dose). (Biogen Inc., 2016)

Off Label Uses
AHFS Drug Information 2019 Edition does not support any off-label uses of Nusinersen (Spinraza).

Experimental, Investigational, Unproven Uses
There is insufficient evidence to support safety and efficacy of nusinersen in SMA Type 0 or 4. No studies evaluating nusinersen enrolled patients older than 18 years of age.

Coding/ Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J2326	Injection, nusinersen, 0.1 mg

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