Spinraza® (Nusinersen)

Policy Number: IEXD0059.11
Effective Date: January 1, 2026

➲ Instructions for Use

Table of Contents **Page**

Related Policies
None

Applicable States

This Medical Benefit Drug Policy applies to Individual Exchange benefit plans in all states except for Massachusetts, Nevada, and New York.

Coverage Rationale

➲ See Benefit Considerations

Spinraza® (nusinersen) is proven and medically necessary for the treatment of spinal muscular atrophy (SMA) in patients who meet all of the following criteria:

Initial Therapy

- Diagnosis of spinal muscular atrophy by, or in consultation with, a neurologist with expertise in the diagnosis of SMA; **and**
- 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:
  - Homozygous gene deletion or mutation (e.g., homozygous deletion of exon 7 at locus 5q13); **or**
  - Compound heterozygous mutation [e.g., deletion of SMN1 exon 7 (allele 1) and mutation of SMN1 (allele 2)]

  and
- Patient is **not** dependent on **either** of the following:
  - Invasive ventilation; **or**
  - Use of non-invasive ventilation beyond use for naps and nighttime sleep

  and
- 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:*
  *Baseline assessments for patients less than 2 months of age are not necessary in order to not delay access to initial therapy in recently diagnosed infants. Initial assessments shortly post-therapy can serve as baseline with respect to efficacy reauthorization assessment:
  - Hammersmith Infant Neurological Exam Part 2 (HINE-2) (infant to early childhood)
  - Hammersmith Functional Motor Scale Expanded (HFMSE)
  - Revised Upper Limb Module (RULM) Test
  - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)

  and

- Spinraza is prescribed by, or in consultation with, a neurologist with expertise in the treatment of SMA; **and**
- **One** of the following:
  - Patient has not previously received gene replacement therapy for the treatment of SMA [e.g., Zolgensma (onasemnogene abeparvovec-xioi)] for; **or**
  - **Both** of the following:
    - Patient has previously received gene replacement therapy [e.g., Zolgensma (onasemnogene abeparvovec-xioi)] for the treatment of SMA; **and**
    - Submission of medical records (e.g., chart notes, laboratory values) documenting a clinically meaningful functional decline (e.g., loss of motor milestone) since receiving gene replacement therapy [e.g., Zolgensma (onasemnogene abeparvovec-xioi)]

  and
- Patient is not receiving concomitant chronic survival motor neuron (SMN) modifying therapy [e.g., Evrysdi (risdiplam)]; **and**
- Spinraza is to be administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures; **and**
- Spinraza dosing for SMA is within accordance with the United States Food and Drug Administration approved labeling; **and**
- Provider does not request a planned inpatient admission for the sole purpose of administering Spinraza; **and**
- Initial authorization will be for no more than four loading doses

Continuation Therapy

- Diagnosis of spinal muscular atrophy by, or in consultation with, a neurologist with expertise in the diagnosis of SMA; **and**
- Patient has previously received Spinraza therapy; **and**
- Patient is **not** dependent on **either** of the following:
  - Invasive ventilation; **or**
  - Use of non-invasive ventilation beyond use for naps and nighttime sleep

  and
- Patient is not receiving concomitant chronic survival motor neuron (SMN) modifying therapy [e.g., Evrysdi (risdiplam)]; **and**
- Submission of medical records (e.g., chart notes, laboratory values) with the most recent results documenting a positive clinical response **from pretreatment baseline status** to Spinraza therapy as demonstrated by at least **one** of the following exams:
  - HINE-2 milestones:
    - **One** of the following:
      - Improvement or maintenance of previous improvement of at least two points (or maximal score) increase in ability to kick; **or**
      - 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; **or**
      - The patient exhibited improvement, or maintenance of previous improvement in more HINE motor milestones than worsening, from pretreatment baseline (net positive improvement); **or**
      - Achieved and maintained any new motor milestones when they would otherwise be unexpected to do so (e.g., sit unassisted, stand, walk)

    or
  - HFMSE: **One** of the following:
    - Improvement or maintenance of previous improvement of at least a three point increase in score from pretreatment baseline; **or**
    - Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so

    or
  - RULM: **One** of the following:
    - Improvement or maintenance of previous improvement of at least a two point increase in score from pretreatment baseline; **or**
    - Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so

    or
  - CHOP INTEND: **One** of the following:
    - Improvement or maintenance of previous improvement of at least a four point increase in score from pretreatment baseline; **or**

    - Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so

and

- Spinraza is prescribed by, or in consultation with, a neurologist with expertise in the treatment of SMA; **and**
- Spinraza is to be administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures; **and**
- Spinraza dosing for SMA is within accordance with the United States Food and Drug Administration approved labeling; **and**
- Provider does not request a planned inpatient admission for the sole purpose of administering Spinraza; **and**
- Reauthorization will be for no more than three maintenance doses (12 months)

Unproven

Spinraza is not proven or medically necessary for:

- Spinal muscular atrophy without chromosome 5q mutations or deletions
- Concomitant treatment of SMA in patients receiving survival motor neuron (SMN) modifying therapy [e.g., Evrysdi (risdiplam)]

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J2326	Injection, nusinersen, 0.1 mg

Diagnosis Code	Description
G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]
G12.1	Other inherited spinal muscular atrophy
G12.9	Spinal muscular atrophy, unspecified

Background

Spinal muscular atrophy (SMA) is a rare, autosomal recessive neuromuscular disease that affects the survival of motor neurons of the spinal cord. SMA is caused primarily by biallelic (homozygous) variants in the SMN1 gene. The estimated annual incidence of SMA is 5.1 to 16.6 cases per 100,000 live births. Approximately 1/40 to 1/60 people are SMA carriers, equating to 3.5 to 5.2 million and 12 to 18 million individuals in the United States and Europe, respectively. SMA is characterized by the degeneration of motor neurons of the spinal cord, resulting in hypotonia and muscle weakness. Historically, SMA has been classified into five phenotypic subtypes (0-4) based on age of symptom onset and motor function achieved. The uncommon SMA type 0 phenotype has prenatal onset associated with decreased fetal movement, significant motor weakness, respiratory distress, difficulty feeding, contractures, and cardiac defects noted at birth. The most incident phenotype, type 1 SMA, occurs in approximately 60% of infants born with SMA with weakness during the first 6 months and never achieving independent sitting. SMA type 2 phenotype has been defined by weakness between 6 and 18 months of life after achieving independent sitting but not walking independently. Approximately 10% of individuals born with SMA presented with SMA type 3 and achieved walking independently with abnormal gait and were diagnosed after 18 months of age. An estimated < 1% of individuals with SMA present during adulthood (usually fourth decade) and are classified as type 4 or adult-onset SMA and have mild motor impairment. Although symptoms are milder and progression is slower, people with adult-onset SMA often experience a long process of testing and evaluations before diagnosis. Current literature indicates that the number of copies of the SMN2 gene that a patient has is the best predictor of clinical phenotype. Individuals with more SMN2 copies usually have a less severe form of SMA than those with fewer copies.

Spinraza® (nusinersen) is a modified antisense oligonucleotide designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Nusinersen binds to a specific sequence in the intron downstream of exon 7 of the SMN2 transcript. Using in vitro assays and studies in transgenic animal models of SMA, nusinersen was

shown to increase exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein. The FDA approved Spinraza on December 23, 2016. According to the FDA, the Spinraza approval was supported by the single pivotal randomized sham-procedure controlled phase 3 study in infantile-onset (Type I) SMA patients. FDA review of open-label trials with Spinraza, while not enough support for FDA approval alone, allowed reasonable extrapolation of benefit of Spinraza for the later onset (Type II and III) SMA subtypes. During the FDA review, the clinical data from the pivotal randomized sham-procedure controlled phase 3 study in later-onset SMA (likely Type II or III) was not reviewed as the trial was ongoing. The manufacturer did provide topline results from interim analysis of the data that along with the open-label data, allowed reasonable extrapolation of benefit to the other SMA subtypes.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

Pre-Symptomatic Patients Likely to Develop Type I SMA

The phase 2 clinical trial (NURTURE) evaluated the effect of Spinraza treatment on pre-symptomatic SMA patients. Twenty-five patients with an SMN1 deletion with two or three copies of SMN2 received Spinraza treatment before 6 weeks of age, in advance of the onset of overt disease symptoms. The NURTURE trial was an eight-year, open-label, single-arm study comparing pre-symptomatic Spinraza efficacy to a control group of affected siblings and natural history data. Based on a 2025 manufacturer press release, at the study conclusion, all children who participated in NURTURE (n = 25) were alive. No participants required permanent ventilation, and the majority (20 of 25 participants) went without any ventilatory support throughout the study.

Type I SMA

An open-label, phase 2, escalating dose clinical study (CS3A) assessed the safety and tolerability, pharmacokinetics, and clinical efficacy of multiple intrathecal doses of nusinersen (6 mg and 12 mg dose equivalents) in patients with infantile-onset spinal muscular atrophy. Eligible participants were of either gender aged between 3 weeks and 7 months old with onset of spinal muscular atrophy symptoms between three weeks and six months, who had SMN1 homozygous gene deletion or mutation. Twenty participants were enrolled between May 3, 2013, and July 9, 2014. In the 12 mg dose group, incremental achievements of motor milestones ($p < 0{\cdot}0001$), improvements in CHOP-INTEND motor function scores ($p = 0{\cdot}0013$), and increased compound muscle action potential amplitude of the ulnar nerve ($p = 0{\cdot}0103$) and peroneal nerve ($p < 0{\cdot}0001$), compared with baseline, were observed. Median age at death or permanent ventilation was not reached and the Kaplan-Meier survival curve diverged from a published natural history case series ($p = 0{\cdot}0014$). Analysis of autopsy tissue from patients exposed to nusinersen showed drug uptake into motor neurons throughout the spinal cord and neurons and other cell types in the brainstem and other brain regions, exposure at therapeutic concentrations, and increased SMN2 mRNA exon 7 inclusion and SMN protein concentrations in the spinal cord. An exposure response analysis of this clinical study suggested that the dose level of 12 mg was more efficacious than 6 mg. This analysis led to an amendment in the phase 3 ENDEAR study in patients with type I SMA to increase the studied dosage regimen to what is currently FDA labeled.

A Phase 3, multicenter, randomized, double-blind, sham-procedure controlled study (ENDEAR study) assessed the clinical efficacy and safety of nusinersen, administered intrathecally in 121 symptomatic infants, ≤ 7 months of age at the time of first dose, diagnosed with SMA (symptom onset before 6 months of age). Patients were randomized 2:1 to receive either nusinersen or sham injection. Patients received nusinersen 12 mg, or sham procedure on day 1, 15, 29, 64 and then maintenance dosing of 12 mg every four months. A planned interim efficacy analysis was conducted based on patients who died, withdrew, or completed at least 183 days of treatment. Of the 82 patients included in the interim analysis, 44% were male and 56% were female. Age at first treatment ranged from 30 to 262 days (median 181). Eighty-seven (87%) of subjects were Caucasian, 2% were Black, and 4% were Asian. Length of treatment ranged from 6 to 442 days (median 261 days). Baseline demographics were balanced between the nusinersen and control groups with the exception of age at first treatment (median age 175 vs. 206 days, respectively). The nusinersen and control groups were balanced with respect to gestational age, birth weight, disease duration, and SMN2 copy number (two copies in 98% of subjects in both groups). Median disease duration was 14 weeks. There was some imbalance in age at symptom onset

with 88% of subjects in the nusinersen group and 77% in the control group experiencing symptoms within the first 12 weeks of life. The primary endpoint assessed at the time of interim analysis was the proportion of responders: patients with an improvement in motor milestones according to Section 2 of the Hammersmith Infant Neurologic Exam (HINE). A treatment responder was defined as any patient with at least a 2-point increase (or maximal score of 4) in ability to kick (consistent with improvement by at least two milestones), or at least a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking (consistent with improvement by at least one milestone). To be classified as a responder, patients needed to exhibit improvement in more categories of motor milestones than worsening. Of the 82 patients who were eligible for the interim analysis, a statistically significantly greater percentage of patients achieved a motor milestone response in the nusinersen group compared to the sham-control group. Fifty-one percent of patients in the nusinersen group achieved the definition of a motor milestone responder compared to 0% of patients in the sham-control group. The primary endpoint assessed at the final analysis was time to death or permanent ventilation (≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event or tracheostomy). Statistically significant effects on event-free survival and overall survival were observed in patients in the nusinersen group compared to those in the sham-control group. A 47% reduction in the risk of death or permanent ventilation was observed in the nusinersen group ($p = 0.005$). Median time to death or permanent ventilation was not reached in nusinersen group and was 22.6 weeks in the sham-control group. A statistically significant 63% reduction in the risk of death was also observed ($p = 0.004$).

Type II/III SMA

An open-label, phase 1 single dose, dose escalation study (CS1) assessed the safety, tolerability, and pharmacokinetics of nusinersen in 28 patients with SMA aged 2 to 14 years. Four dose cohorts were evaluated. Patients received a single dose of 1 mg, 3 mg, 6 mg, or 9 mg and were evaluated at day 29 and 85 for the 6 mg and 9 mg dosing cohorts. The mean change in HFMSE from baseline in the 9 mg single dose cohort at day 29 and 85 was 2.4 and 3.1 respectively.

An open-label, phase 1 single dose study (CS10) assessed the safety, tolerability, and pharmacokinetics of a single subsequent dose nusinersen in patients with SMA who previously participated in the CS1 study. Patients were to receive either 6 mg or 9 mg of nusinersen, however the study was amended after four subjects were enrolled to a single 9 mg dose. Patients were to receive a subsequent nusinersen dose 9 to 15 months after the initial dose in the CS1 study. Eighteen patients were enrolled, eight of which were in the 9 mg cohort 4 in CS1. The mean change in HFMSE from CS1 baseline in the 8 CS1 cohort 4 patients was 5.8 9-14 months after initial dosing in CS1. The mean change in HFMSE from CS1 baseline at approximately 15 to 18 months after two 9 mg doses of nusinersen was 6.1.

An open-label, dose escalation study (CS2 study) assessed the safety, tolerability, and dose range of nusinersen in SMA patients aged 2 to 15 years. Four dose cohorts (3, 6, 9, and 12) were evaluated. Cohort 1 (3 mg), 2 (6 mg), and 4 (12 mg) received nusinersen on days 1, 29, and 85). Cohort 3 (9 mg) received nusinersen on days 1 and 85. Exploratory efficacy variables included HFMSE, Pediatric Quality of Life Inventory, compound muscle action potential (CMAP) and motor unite number estimation (MUNE), the Upper Limb Module test (ULMT), muscle strength using hand-held dynamometry, the 6-minute Walk Test (6MWT), and the Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) questionnaire. Cohorts 1, 2, and 4 each had 8 patients and cohort 3 had 9 patients. Subjects were evaluated using the HFMSE at Baseline and on Days 92, 169, and 253. An efficacy evaluable population was also identified, this population included patients whose baseline HFMSE score was between 10 and 54. The largest mean HFMSE change from baseline was seen in cohort 3, with a mean change of 2.7, 2.9, and 3.7 at days 92, 169, and 253 respectively. The mean HFMSE change in cohort 4 was 0.6, 1.0, and 2.3 at days 92, 169, and 253 respectively. In the efficacy evaluable population, the mean change in cohort 3 ($n = 8$) was 2.7, 3.1, and 3.9 at days 92, 169, and 253 respectively. In the efficacy evaluable population, the mean change in cohort 4 ($n = 5$) was 1.8, 2.0, and 3.8 at days 92, 169, and 253 respectively. According to the FDA, there appeared to be a consistent trend of increasing HFMSE over time with nusinersen treatment in the 6 mg, 9 mg, and 12 mg cohorts.

An open-label phase 1 study (CS12) assessed the safety, tolerability, and efficacy of maintenance nusinersen in 47 patients who previously participated in either the CS2 or CS10 trial. Patients received 12 mg nusinersen at six-month intervals and were expected to participate in CS12 for up to approximately two years. Efficacy parameters included the change in HFMSE, 6MWT, and ULMT. At day 624 the mean change in HFMSE was 0.47, at day 715, the median change in HFMSE was 0. Median scores were reported at day 715 due to a single outlier. At day 715 the mean change in ULMT was 1.0. At day 624, among the 22 patients with type III SMA who were ambulatory at baseline, the mean change in 6MWT was 26.13 meters.

A Phase 3 multicenter, double-blind, randomized, sham-procedure controlled study (CHERISH) assessed the clinical efficacy and safety of nusinersen in patients with later-onset SMA consistent with Type II or Type III SMA. Subjects were randomized 2:1 to receive intrathecal nusinersen or a sham procedure control, respectively. Patients received nusinersen 12 mg loading dose, or sham procedure on day 1, 29, 85 and then maintenance dosing of 12 mg six months after the last

dose on day 274. The loading dose level and interval was selected based on the nonclinical pharmacokinetic and pharmacology data as the dose interval to achieve and maintain nusinersen spinal cord tissue levels that are predicted to be within the upper end of the pharmacologically active range following the first dose (predicted to be approximately 24 mcg/g lumbar and 8 mcg/g cervical tissue concentration at day 85), while at the same time considering subject safety and convenience for repeated LP intrathecal injections. The maintenance dose interval (once every six months) was selected based on the estimated spinal tissue and CSF drug half-life (four to six months) and was selected to maintain spinal cord tissue levels of nusinersen at a steady-state level within the estimated pharmacologically active range. The CHERISH protocol was drafted, and thus the study regimen was selected, after the ENDEAR study amendment that increased the dosing frequency in patient with type 1 SMA. Inclusion criteria included diagnosis with SMA with clinical signs and symptoms consistent with SMA at greater than 6 months of age, an age of 2 to 12 years, the ability to sit independently, but never able to walk independently (defined as the ability to walk ≥ 15 ft. unaided) and have a HFMSE score greater than or equal to 10 and less than or equal to 54 at Screening. The primary endpoint was change from baseline in HFMSE score (at 15 months). Secondary Endpoints were (at 15 months): proportion of subjects who achieve a 3-point increase from baseline in HFMSE score, proportion of subject that achieve any new motor milestone, number of motor milestones achieved per subject, change from baseline in Upper Limb Module Test, proportion of subjects that achieve standing alone, proportion of subject that achieve walking with assistance. 126 children were enrolled in the trial with 84 receiving nusinersen. 90% of children had an SMN2 copy number of three or greater. In the pre-planned interim analysis, a significant difference ($p = 0.0000002$) of 5.9 points in HFMSE was observed at 15 months between patients given nusinersen ($n = 84$) compared to the sham-procedure control ($n = 42$) and the study was stopped early. Patients receiving nusinersen experienced a mean improvement of 4.0 points in the HFMSE compared to a mean decrease of 1.9 points in the sham procedure control group in the interim analysis. In the final analysis, Patients receiving nusinersen experienced a mean improvement of 3.9 points in the HFMSE compared to a mean decrease of 1.0 points in the sham procedure control group. A change of ≥ 3 points in the HFMSE has previously been determined to be clinically important. Subgroup analysis showed similar efficacy of nusinersen in type II/III SMA patients regardless of SMN2 copy number. 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 ($p < 0.001$) The percentage of children who achieved at least one new motor milestone did not differ significantly between the nusinersen group and the control group. The proportion of children who had achieved the ability to stand alone or walk with assistance did not differ significantly between groups. Adverse events were mostly considered to be related to SMA disease, common events found in the general population, or events related to the lumbar puncture procedure. No patients discontinued the study. Nusinersen was well tolerated with a favorable safety profile.

At the time of FDA approval, review of the nusinersen clinical development program, including the open label phase 2 trial (CS12), the blinded phase 3 [CS4 (CHERISH)] trial, or the open-label phase 2 extension trial [CS11 (SHINE)] identified that all patients who had later-onset SMA received maintenance treatment with nusinersen at six-month intervals, less than that listed in the FDA label. FDA review of patients in the CS12 trial, along with review of the recently published phase 3 data showed documented improvement in outcome measures, such as HFMSE, over the three years of available data with these later-onset SMA patients. Analysis of the early phase 1/2 studies (CS1, CS2, CS10, CS12), where a variety of different dosage regimens were studied in patients with later-onset SMA, appears to show the responses to nusinersen are seen early after nusinersen administration and remained stable across a variety of dosage regimens. To date, no randomized clinical trial in patients with later-onset SMA has evaluated nusinersen at a dose intensity or frequency greater than what has been described in the CHERISH trial.

Professional Societies

American Academy of Neurology/American Academy of Pediatrics

In 2018, the American Academy of Neurology published systematic review of the evidence for the use of nusinersen in spinal muscular atrophy. In addition, the American Academy of Pediatrics endorsed this publication. The systematic review resulted in the following: Four published clinical trials were identified, 3 of which were rated above Class IV. There is Class III evidence that in infants with homozygous deletions or mutations of SMN1, nusinersen improves the probability of permanent ventilation-free survival at 24 months vs a well-defined historical cohort. There is Class I evidence that in term infants with SMA and two copies of SMN2, treatment with nusinersen started in individuals younger than 7 months results in a better motor milestone response and higher rates of event-free survival than sham control. There is Class I evidence that in children aged 2–12 years with SMA symptom onset after 6 months of age, nusinersen results in greater improvement in motor function at 15 months than sham control. Nusinersen was safe and well-tolerated. The authors concluded that the evidence of efficacy is currently highest for treatment of infantile- and childhood-onset SMA in the early and middle symptomatic phases. While approved indications for nusinersen use in North America and Europe are broad, payer coverage for populations outside those in clinical trials remain variable. Evidence, availability, cost, and patient preferences all influence decision making regarding nusinersen use.

In the 2018 Cure SMA Working Group treatment algorithm, the working group stresses the need for early intervention through newborn screening to maximize the benefit of treatment. The group recommends the development of dependable and validated screening techniques to enable treatment of presymptomatic patients who may be more responsive to treatment than those already experiencing symptoms. For patients with SMA Types II or III with three or fewer copies of the *SMN2* gene, the group recommends immediate treatment with a disease modifying therapy and referral to both a neuromuscular specialist and a geneticist; for those with only one copy of *SMN2* who are symptomatic at birth, the group states that the attending physician should determine whether the patient and family would benefit from treatment. Lastly, patients with four copies of *SMN2* should be screened periodically for symptoms and referred to a geneticist to determine the exact number of *SMN2* copies, but the working group recommends against immediate treatment with a disease modifying therapy.

In September 2019, Cure SMA reconvened the multidisciplinary working group to reassess the treatment algorithm for newborns with SMA identified through newborn screening based upon new experience and therapeutic options. The working group has updated their position to a recommendation for immediate treatment for infants diagnosed with SMA via NBS with four copies of SMN2. The working group also revisited the published recommendation to wait to treat for infants with five copies of SMN2 and unanimously voted to uphold the recommendation of watchful waiting. The working group acknowledged that current laboratory assays designed to detect SMN2 copy number often have difficulty distinguishing high copy numbers of SMN2 and that many laboratories report results as four or more SMN2 copies, being unable to give an exact number. Recognizing this fact, the working group encouraged follow-up with a laboratory able to distinguish exact SMN2 copy number.

Health Care Provider Working Group

An SMA working group of American and European health care providers updated the SMA best practice recommendations for diagnosis through systematic literature review and sequential modified Delphi surveys and discussions. The Health care provider working group (HCPWG), supported by Cure SMA, included 18 members plus 2 organizing and nonvoting Cure SMA staff members who moderated discussions and had no stake in the decisions. The HCPWG included 5 European physician neurologists, 12 US physician neurologists, and 1 U.S. genetic counselor. All HCPWG members participated voluntarily without compensation. Included in their recommendations was a recommendation that SMA infants identified by NBS and before treatment initiation should be characterized by SMN2 copy number, current motor function, age at symptom onset, and severity of symptoms. The classification of SMA severity based on SMA type has changed due to the effectiveness of SMN-enhancing treatments in tandem with early identification by NBS and urgent confirmatory diagnosis. Thus, the HCPWG discussed that classification of newborns by SMA type is not clinically meaningful for newly diagnosed infants with SMA and those treated early in their life with SMN-enhancing treatment(s). Because SMN2 copy number is associated with disease phenotype, progression, and outcomes, determining the number of SMN2 copies is urgent and should be included as a component of the confirmatory diagnostic testing to include both the number of SMN1 and SMN2 gene copies. In addition, based on consensus recommendations by US clinicians to treat infants with 4 copies of SMN2 urgently, distinguishing between 4 and 5 copies of SMN2 is necessary.

2024 Update: European Consensus Statement on Gene Therapy for Spinal Muscular Atrophy

In 2020, a group of 13 European neuromuscular experts, conveyed to help aid the rational use of Zolgensma and presented 11 consensus statements covering qualification, patient selection, safety considerations and long-term monitoring after the European Medical Agency (EMA) approval of Zolgensma. After three years, a similar yet larger group of European experts assembled and assessed the emerging evidence of onasemnogene abeparvovec's role in treating older and heavier SMA patients, integrating insights from recent clinical trials and real-world evidence. This effort resulted in 12 consensus statements, with strong consensus achieved on 9 and consensus on the remaining 3, reflecting the evolving role of onasemnogene abeparvovec in treating SMA.

In the 2024 update, the group stated in revised consensus statement 6: “In absence of convincing evidence of published superiority of the combination of two disease-modifying treatments (e.g., gene therapy and nusinersen; or gene therapy and risdiplam), combinatorial therapies cannot be recommended at the moment. A controlled clinical trial setting with head-to-head-comparison of one vs. two disease-modifying treatments is regarded as gold-standard to answer this open question.”

Consensus statement 6 comment: “Besides nusinersen, risdiplam has been available since 2021 as an additional disease-modifying treatment for SMA and has therefore been included in the statement. Risdiplam is an orally administered small molecule, that enhances SMN protein production by modifying the splicing of the SMN2 gene. Several combinations of disease-modifying treatments have been reported in the real world, and classifications that define

"bridging" (using temporary nusinersen or risdiplam before gene therapy), "adding" and "switching" have been proposed. While bridging might be appropriate in specific situations where one therapy is not readily available, our statement refers to the simultaneous use of two treatments. Although some clinical trials and publications report on the combination of different disease-modifying treatments (e.g., nusinersen or risdiplam after onasemnogene abeparvovec), they do not conclusively prove that a combination is superior to any single treatment due to the lack of an adequate control group. Since all three approved treatments primarily exert their effects by increasing SMN protein levels, it remains questionable whether there is an additive benefit when targeting motor neurons. In addition, the significant cost of disease-modifying treatments questions the cost-effectiveness and the sustainability of this strategy, especially when the cost of the drug is added to the cost of standard of care."

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Spinraza is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

References

1. Spinraza [package insert]. Cambridge, MA: Biogen, Inc, April 2024.
2. Food and Drug Administration. Spinraza medical review. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209531Orig1s000MedR.pdf. December 15, 2016. Accessed February 28, 2018.
3. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. n Engl J Med. 2018 Feb 15;378(7):625-635.
4. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. n Engl J Med. 2017 Nov 2;377(18):1723-1732.
5. Markowitz JA, Singh P, Darras BT. Spinal Muscular Atrophy: A Clinical and Research Update. Pediatric Neurology 46 (2012) 1-12.
6. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of > 72,400 specimens. Eur J Hum Genet 2012;20:27-32.
7. Prior TW, Snyder PJ, Rink BD, et al. Newborn and carrier screening for spinal muscular atrophy. Am J Med Genet A. 2010 Jul;152A(7):1608-16.
8. Lunn MR, Wang CH. Spinal muscular atrophy. Lancet. 2008 Jun 21;371(9630):2120-33.
9. 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. 2017 Dec 17;388(10063):3017-3026.
10. Chiriboga CA, Swoboda KJ, Darras BT, et al. Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy. Neurology. 2016 Mar 8;86(10):890-7.
11. Haataja L, Mercuri E, Regev R, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J Pediatr. 1999 Aug;135(2 Pt 1):153-61.
12. Glanzman AM, O'Hagen JM, McDermott MP, et al. Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III. J Child Neurol. 2011;26(12):1499-507.
13. O'Hagen JM, Glanzman AM, McDermott MP, et al. An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. Neuromuscular disorders: NMD. 2007;17(9-10):693-7.
14. Isis pharmaceuticals initiates SHINE study to provide ISIS-SMN Rx for patients with SMA who have completed the Phase 3 ENDEAR and CHERISH studies. https://www.prnewswire.com/news-releases/isis-pharmaceuticals-initiates-shine-study-to-provide-isis-smn-rx-for-patients-with-sma-who-have-completed-the-phase-3-endear-and-cherish-studies-300160957.html. Accessed March 14, 2022.
15. Spinraza [AMCP dossier]; Cambridge, MA: Biogen; December 2016.
16. Protocol for: Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. n Engl J Med 2018;378:625-35. DOI: 10.1056/NEJMoa1710504.

17. Protocol for: Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. n Engl J Med 2017;377:1723-32. DOI: 10.1056/NEJMoa1702752.
18. An Open-Label Extension Study for Patients With Spinal Muscular Atrophy Who Previously Participated in Investigational Studies of ISIS 396443. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT02594124?term=NCT02594124&rank=1. Accessed March 28, 2023.
19. Calucho M, Bernal M, Alias L, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscular disorders. 2018; 28:208-15.
20. A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy (NURTURE). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT02386553?term=nusinersen+nurture&rank=1. Accessed April 3, 2024.
21. Hwu W, De D, Bertini E, et al. Outcomes after 1-year in presymptomatic infants with genetically diagnosed spinal muscular atrophy (SMA) treated with nusinersen: interim results from the NURTURE study. Neuromuscul Disord. 2017;27(Supplement 2):S212.
22. Swoboda KJ, Scott CB, Crawford TO, et al. SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy. PLoS One 2010;5(8): e12140.
23. Kaufmann P, McDermmott MP, Darras DT, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. Neurology. 2012; 79:1889-97.
24. Mercuri E, Finkel RS, Montes J, et al. Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials. Neuromuscular Disorders. 2016; 26:126-131.
25. Michelson D, Ciafaloni E, Ashwal S, et al. Evidence in focus: Nusinersen use in spinal muscular atrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018 Nov 13;91(20):923-933.
26. Glascock J SJ, Haidet-Phillips A, et al. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. Journal of Neuromuscular Diseases. 2018;5(2):145–158.
27. Glascock J, Sampson J, Connolly AM, et al. Revised Recommendations for the treatment of infants diagnosed with spinal muscular atrophy via newborn screening who have 4 copies of SMN2. Journal of Neuromuscular Diseases. 2020; vol. Pre-press, no. Pre-press, pp. 1-4, 2020. https://doi.org/10.3233/JND-190468.
28. Kirschner J, Butoianu N, Goemans N, et al. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. European Journal of Paediatric Neurology. 2020, doi: https://doi.org/10.1016/j.ejpn.2020.07.001.
29. A Study of Nusinersen Among Participants With Spinal Muscular Atrophy Who Received Onasemnogene Abeparvovec-xioi ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT04488133?term=nusinersen&draw=2&rank=1. Accessed April 3, 2024.
30. Pera MC, Coratti G, Mazzone ES, Montes J, Scoto M, De Sanctis R, Main M, Mayhew A, Muni Lofra R, Dunaway Young S, Glanzman AM, Duong T, Pasternak A, Ramsey D, Darras B, Day JW, Finkel RS, De Vivo DC, Sormani MP, Bovis F, Straub V, Muntoni F, Pane M, Mercuri E; iSMAC Consortium Group. Revised upper limb module for spinal muscular atrophy: 12 month changes. Muscle Nerve. 2019 Apr;59(4):426-430. doi: 10.1002/mus.26419. Epub 2019 Feb 7. PMID: 30677148.
31. Stolte B, Bois JM, Bolz S, Kizina K, Totzeck A, Schlag M, Kleinschnitz C, Hagenacker T. Minimal clinically important differences in functional motor scores in adults with spinal muscular atrophy. Eur J Neurol. 2020 Dec;27(12):2586-2594. doi: 10.1111/ene.14472. Epub 2020 Sep 6. PMID: 32781490.
32. Kirschner J, Bernert G, Butoianu N, et al. 2024 update: European consensus statement on gene therapy for spinal muscular atrophy. Eur J Paediatr Neurol. 2024;51:73-78. doi:10.1016/j.ejpn.2024.06.0013.
33. Schroth M, Deans J, Arya K, et al. Spinal Muscular Atrophy Update in Best Practices: Recommendations for Diagnosis Considerations. Neurol Clin Pract. 2024;14(4):e200310. doi:10.1212/CPJ.0000000000200310.
34. Biogen Inc. New Data for Nusinersen Underscore Biogen's Commitment to Advancing Clinical Research to Improve Outcomes in SMA. Biogen Newsroom. Published June 27, 2025. Accessed October 8, 2025. https://investors.biogen.com/news-releases/news-release-details/new-data-nusinersen-underscore-biogens-commitment-advancing.

Policy History/Revision Information

Date	Summary of Changes
01/01/2026	**Coverage Rationale** • Revised coverage criteria; added criterion requiring the provider does not request a planned inpatient admission for the sole purpose of administering Spinraza **Supporting Information** • Updated *Background*, *Clinical Evidence*, and *References* sections to reflect the most current information • Archived previous policy version IEXD0059.10

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.