Spinraza® (Nusinersen) (for Pennsylvania Only)

Policy Number: CSPA2023D0059K
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Instructions for Use

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Related Policies

None

Application

This Medical Benefit Drug Policy only applies to the state of Pennsylvania.

Coverage Rationale

Spinraza® (nusinersen) is proven and medically necessary for the treatment of spinal muscular atrophy (SMA) in patients who meet all of the following criteria:[1-4,22,23]

- For **initial therapy**, **all** of the following:
  - 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 following:
    - 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);[1,5] **or**
      - Compound heterozygous mutation (e.g., deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 [allele 2])

    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)[1,8,12] (infant to early childhood)
    - Hammersmith Functional Motor Scale Expanded (HFMSE)[1,9,13-14]
    - Upper Limb Module (ULM) Test (Non ambulatory)[1,9]
    - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)[1,8]

    and
  - Spinraza is prescribed by, or in consultation with, a neurologist with expertise in the treatment of SMA; **and**
  - Patient has not previously received gene replacement therapy for the treatment of SMA; **or**
    - **One** of the following:
      - **Both** of the following:

- Patient recently received gene replacement therapy within the previous 6 months; **and**
- Patient has experienced a declination in clinical status since receipt of gene replacement therapy

or

– **Both** of the following:
- Patient has previously received gene replacement therapy; **and**
- Patient has experienced a declination in clinical status that represents a potential abatement of gene therapy efficacy

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 in accordance with the United States Food and Drug Administration approved labeling; **and**
- Initial authorization will be for no more than 4 loading doses

- For **continuation therapy**, **all** of the following:
  - 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 has not previously received gene replacement therapy for the treatment of SMA; **or**
    - **Both** of the following:
      – Patient has previously received gene replacement therapy; **and**
      – Patient has experienced a declination in clinical status that represented a potential failure or abatement of gene therapy efficacy

      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 (< 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:
    - HINE-2 milestones:
      – **One** of the following:
        - Improvement or maintenance of previous improvement in ability to kick
        - Improvement or maintenance of previous improvement in any other HINE-2 milestone (e.g., head control, rolling, sitting, crawling, etc.), excluding voluntary grasp
        - Continued clinical benefit based on the prescriber's assessment

      and
      – **One** of the following:
        - The patient exhibited improvement, or maintenance of previous improvement in more HINE motor milestones than worsening, from pretreatment baseline (net positive improvement)
        - Achieved and maintained any new motor milestones when they would otherwise be unexpected to do so (e.g., sit unassisted, stand, walk)
        - Continued clinical benefit based on the prescriber's assessment

      or
    - HFMSE**: One** of the following:
      – Improvement or maintenance of previous improvement in score from pretreatment baseline
      – Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so
      – Continued clinical benefit based on the prescriber's assessment

      or
    - ULM: **One** of the following:
      – Improvement or maintenance of previous improvement in score from pretreatment baseline
      – Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so
      – Continued clinical benefit based on the prescriber's assessment

      or

- CHOP INTEND: **One** of the following:
  - Improvement or maintenance of previous improvement in score from pretreatment baseline
  - Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so
  - Continued clinical benefit based on the prescriber's assessment

  or
- **Both** of the following:
  - Patient was prescribed Spinraza due to clinical declination after receipt of gene therapy; **and**
  - Continued clinical benefit based on the prescriber's assessment

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 in accordance with the United States Food and Drug Administration approved labeling; **and**
- Reauthorization will be for no more than 3 maintenance doses (12 months)

Unproven

Spinraza is not proven or medically necessary for:[1]

- Spinal muscular atrophy without chromosome 5q mutations or deletions
- Routine concomitant treatment of SMA in patients who have previously received gene replacement therapy

Requests outside of this criteria will be reviewed for medical necessity on a case-by-case basis.

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 federal, state, or contractual requirements 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.[5] SMA is caused by the deletion/mutation of the SMN1 gene.[5] 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.[6-9] SMA is characterized by the degeneration of motor neurons of the spinal cord, resulting in hypotonia and muscle weakness. Five phenotypic subtypes of SMA (0-IV) have been described based on age of symptom onset and motor function achieved.[8] Current literature indicates that the number of copies of the SMN2 gene that a patient has is the best predictor of clinical phenotype. The table below summarizes the clinical and genetic characteristics of the SMA subtypes.[2,5,8,21]

Clinical SMA Diagnosis	% of SMA Cases	Usual Number of SMN2 Copies	Typical Age of Symptom Onset	Life Expectancy	Motor Development
Type 0	Very rare	1	In utero	Death occurs shortly after birth	None
Type I	58%	2	< 6 months	< 24 months	Never able to sit
Type II	29%	2-4 (80% have 3 copies)	< 18 months	70% alive at 25 years	Unable to walk without assistance
Type III	13%	95% have ≥ 3 copies		May be normal	Able to stand and walk without assistance, but lose ability as disease progresses
Type IV	< 5%	≥ 4	20-30 years	Normal	Ambulatory. May experience mild muscle weakness

The severity of the clinical phenotype is heterogenous with the most severe form, type I SMA, occurring in infancy. The median survival of a patient with type I SMA is 7 months. The later-onset forms, type II and type III, cause a less severe motor disability. The Hammersmith Functional Motor Score Expanded (HFMSE) is a common assessment tool used to evaluate later-onset SMA. The HFMSE is a 33-item measure of motor function that is specifically validated for use in patients with SMA to assess activities related to daily living. The total score can range from 0-66 with higher scores indicating better motor function. A change in HFMSE score of at least 3 points is considered clinically meaningful.[26] The natural history of patients with type II/III SMA has been described in two recent publications. A 2012 study reported a mean HFMSE decline of -0.54 over 2 years in type 2 SMA.[27] A 2016 publication attempted to describe the patterns of disease progression for patients with type 2/3 SMA. The results obtained in 268 patients found that patients show small mean changes over a 12-month period on the HFMSE. The vast majority of patients (over 75%) had changes ±2 points, with less than 10% showing an improvement of more than 2 points, in agreement with previously reported data.[28]

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.[1] 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.[2]

Clinical Evidence

Pre-Symptomatic Patients Likely to Develop Type I SMA

An ongoing phase 2 clinical trial (NURTURE) is evaluating the effect of Spinraza treatment on pre-symptomatic SMA patients.[22] 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 is an open-label, single-arm study comparing pre-symptomatic Spinraza efficacy to a control group of affected siblings and natural history data. An interim analysis was performed after all patients had received Spinraza for 14 months (median 25 months, range 14 to 34 months). At the time of interim analysis (data cutoff May 2018), all patients receiving Spinraza before the onset of SMA symptoms survived without requiring permanent ventilation, and beyond what would be expected based on their SMN2 copy number. All 25 patients (100%) had achieved the WHO motor milestone of sitting without support, and 22 patients (88%) had achieved the milestone of

walking with assistance. Of the 22 patients who were older than the age expected to have achieved the ability to walk independently (as defined by the 95th percentile of the WHO expected age of achievement), 17 (77%) achieved the milestone of walking alone (i.e., walking independently).[1,23]

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 3 weeks and 6 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 12mg, or sham procedure on day 1, 15, 29, 64 and then maintenance dosing of 12 mg every 4 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 (2 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 2 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 1 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.[1,4] 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 ($p = 0.004$).[1, 4]

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

either 1 mg, 3 mg, 6 mg, or 9 mg and were evaluated at day 29 and 85 for the 6mg 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 4 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 6mg, 9mg, and 12mg 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 6-month intervals and were expected to participate in CS12 for up to approximately 2 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 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 6 months) was selected based on the estimated spinal tissue and CSF drug half-life (4-6 months) and was selected to maintain spinal cord tissue levels of nusinersen at a steady-state level within the estimated pharmacologically active range.[18] 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 $\geq$ 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 3 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.[2,3]

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 6 month intervals, less than that listed in the FDA label.[2,16,17] 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 3 years of available data with these later-onset SMA patients. [2] 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 be 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.[29] 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 2 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.[30]

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.[31]

2020 European Neuromuscular Expert Ad-Hoc Consensus Statement on Gene Replacement Therapy for Spinal Muscular Atrophy [32]

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. A consensus greater than 95% was considered "strong consensus", between 75 and 95% "consensus", and between 50 and 75% "majority consensus". If less than 50% approved a statement, it was labelled as "no consensus". A statement regarding combination therapy and discussion of the rationale was among these 11 consensus statements.

The group stated with a 100% consensus that "Until now there is no published evidence that a 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 biodistribution 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."

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.

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Policy History/Revision Information

Date	Summary of Changes
7/1/2023	**Supporting Information** • Updated *References* section to reflect the most current information • Archived previous policy version CSPA2022D0059J

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. 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. The 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.