

SPINRAZA™ (NUSINERSEN)

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Table of Contents	Page
INSTRUCTIONS FOR USE	1
BENEFIT CONSIDERATIONS	1
COVERAGE RATIONALE	2
U.S. FOOD AND DRUG ADMINISTRATION	3
BACKGROUND	3
APPLICABLE CODES	3
CLINICAL EVIDENCE	4
CENTERS FOR MEDICARE AND MEDICAID SERVICES	5
REFERENCES	5
POLICY HISTORY/REVISION INFORMATION	5

Related Policies
None

INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Drug Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Drug Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This 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 MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines 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.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

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. See the Policy and Procedure addressing the treatment of serious rare diseases.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

Spinraza™ (nusinersen) is proven and medically necessary for:¹

- I. The treatment of **Spinal Muscular Atrophy (SMA)** in patients who meet **all** of the following criteria:
- A. For **initial therapy**, **all** of the following:
1. Diagnosis of spinal muscular atrophy type I, II, or III by, or in consultation with, a neurologist with expertise in the diagnosis of SMA.
and
 2. Submission of medical records (e.g., chart notes, laboratory values) confirming **both** of the following:
 - a. The mutation or deletion of genes in chromosome 5q resulting in **one** of the following:
 - i. Homozygous gene deletion or mutation (e.g., homozygous deletion of exon 7 at locus 5q13)^{1,2}; **or**
 - ii. Compound heterozygous mutation (e.g., deletion of SMN1 exon 7[allele 1] and mutation of SMN1 [allele 2])
and
 - b. Patient has at least 2 copies of SMN2
and
 3. Patient is **not** dependent on **either** of the following:
 - a. Invasive ventilation or tracheostomy
 - b. Use of non-invasive ventilation beyond use for naps and nighttime sleep
and
 4. Submission of medical records (e.g., chart notes, laboratory values) of the baseline exam of at least **one** of the following exams (based on patient age and motor ability) to establish baseline motor ability:
 - a. Hammersmith Infant Neurological Exam Part 2 (**HINE-2**)^{1,8,12} (infant to early childhood)
 - b. Hammersmith Functional Motor Scale Expanded (**HFMSE**)^{1,9,13-14}
 - c. Upper Limb Module (**ULM**) Test (Non ambulatory)^{1,9},
 - d. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (**CHOP INTEND**)^{1,8}
and
 5. Spinraza is prescribed by, or in consultation with, a neurologist with expertise in the treatment of SMA
and
 6. Spinraza is to be administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures; **and**
 7. Spinraza dosing for SMA is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 12mg for each loading dose; **and**
 8. Initial authorization will be for no more than 4 loading doses.
- B. For **continuation therapy**, **all** of the following:
1. Diagnosis of spinal muscular atrophy type I, II, or III by, or in consultation with, a neurologist with expertise in the diagnosis of SMA.
and
 2. Submission of medical records (e.g., chart notes, laboratory values) confirming **both** of the following:
 - a. The mutation or deletion of genes in chromosome 5q resulting in **one** of the following:
 - i. Homozygous gene deletion or mutation (e.g., homozygous deletion of exon 7 at locus 5q13)^{1,2}; **or**
 - ii. Compound heterozygous mutation (e.g., deletion of SMN1 exon 7[allele 1] and mutation of SMN1 [allele 2])
and
 - b. Patient has at least 2 copies of SMN2
and
 3. Patient is **not** dependent on **either** of the following:
 - a. Invasive ventilation or tracheostomy
 - b. Use of non-invasive ventilation beyond use for naps and nighttime sleep
and
 4. 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:
 - a. **HINE-2** milestones :
 - i. **One** of the following:
 - 1) Improvement or maintenance of previous improvement of at least 2 point (or maximal score) increase in ability to kick
 - 2) Improvement or maintenance of previous improvement of at least 1 point increase in any other HINE-2 milestone (e.g., head control, rolling, sitting, crawling, etc.), excluding voluntary grasp
and

- ii. **One** of the following:
 - 1) The patient exhibited improvement, or maintenance of previous improvement in more HINE motor milestones than worsening, from pretreatment baseline (net positive improvement)
 - 2) Achieved and maintained any new motor milestones when they would otherwise be unexpected to do so (e.g., sit unassisted, stand, walk)
- or**
- b. **HFMSE: One** of the following:
 - i. Improvement or maintenance of previous improvement of at least a 3 point increase in score from pretreatment baseline
 - ii. Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so
- or**
- c. **ULM: One** of the following:
 - i. Improvement or maintenance of previous improvement of at least a 2 point increase in score from pretreatment baseline
 - ii. Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so
- or**
- d. **CHOP INTEND: One** of the following:
 - i. Improvement or maintenance of previous improvement of at least a 4 point increase in score from pretreatment baseline
 - ii. Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so
- and**
- 5. Spinraza is prescribed by, or in consultation with, a neurologist with expertise in the treatment of SMA; **and**
- 6. Spinraza is to be administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures; **and**
- 7. Spinraza dosing for SMA is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 12mg every 4 months, starting 4 months after the last loading dose; **and**
- 8. Reauthorization will be for no more than 3 maintenance doses (12 months).

Spinraza is not proven or medically necessary for spinal muscular atrophy without chromosome 5q mutations or deletions.¹

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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.

BACKGROUND

Spinal muscular atrophy (SMA) is a rare, autosomal recessive neuromuscular disease that affects the survival of motor neurons of the spinal cord.² SMA is caused by the deletion/mutation of the SMN1 gene.² 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.³⁻⁶ SMA is characterized by the degeneration of motor neurons of the spinal cord, resulting in hypotonia and muscle weakness. Five subtypes of SMA (0-IV) have been described based on age of symptom onset and motor function achieved.⁷

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

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 Coverage Determination Guidelines may apply.

HCPCS Code	Description
J2326	Injection, nusinersen, 0.1 mg

ICD-10 Diagnosis Code	Description
G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]
G12.1	Other inherited spinal muscular atrophy

CLINICAL EVIDENCE

A Phase III, multicenter, randomized, double-blind, sham-procedure controlled study assessed the clinical efficacy and safety of nusinersen, administered intrathecally in 121 symptomatic infants, \leq 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. 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. A significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (21 of 51 infants [41%] vs. 0 of 27 [0%], $P < 0.001$), resulting in the early termination of the trial. In the final analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (37 of 73 infants [51%] vs. 0 of 37 [0%]), and the likelihood of event-free survival was higher in the nusinersen group than in the control group (hazard ratio for death or the use of permanent assisted ventilation, 0.53; $P = 0.005$). The likelihood of overall survival was higher in the nusinersen group than in the control group (hazard ratio for death, 0.37; $P = 0.004$), and infants with a shorter disease duration at screening were more likely than those with a longer disease duration to benefit from nusinersen. The incidence and severity of adverse events were similar in the two groups. The authors concluded that infants with SMA who received nusinersen were more likely to be alive and have improvements in motor function than those in the control group. The authors suggested that early treatment may be necessary to maximize the benefit of the drug.^{1, 8}

A Phase III 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 SMA. Subjects were randomized 2:1 to receive intrathecal nusinersen or a sham procedure control, respectively. Inclusion criteria included diagnosis with SMA, have clinical signs and symptoms consistent with SMA at greater than 6 months of age, be able to sit independently, but never able to walk independently and have a HFMSE score greater than or equal to 10 and less than or equal to 54 at Screening. The primary endpoint is change from baseline in HFMSE score (at 15 months). Secondary Endpoints are (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. In a 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 ($n = 42$). 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 (5). A change of ≥ 3 points in the HFMSE has previously been determined to be clinically important. Results for other endpoints were consistent with a favorable response to nusinersen compared to sham-procedure control. 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.⁹

The results of the controlled trial in infantile-onset SMA patients were supported by open-label uncontrolled trials conducted in symptomatic SMA patients who ranged in age from 30 days to 15 years at the time of first dose, and in

presymptomatic patients, who ranged in age from 8 days to 42 days at the time of first dose. The patients in these studies had or were likely to develop Type 1, 2, or 3 SMA. Some patients achieved milestones such as ability to sit unassisted, stand, or walk when they would otherwise be unexpected to do so, maintained milestones at ages when they would be expected to be lost, and survived to ages unexpected considering the number of SMN2 gene copies of patients enrolled in the studies.^{10,11}

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for SPINRAZA™ (nusinersen). Local Coverage Determinations (LCDs) do not exist at this time.

Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals at <http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf>. (Accessed February 13, 2018)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
04/01/2018	Annual review. Updated coverage rationale without change in clinical intent. Updated clinical evidence, CMS statement, and references. Approved by National Pharmacy & Therapeutics Committee on 03/21/2018. Policy 2018D0059C archived.
01/01/2018	<ul style="list-style-type: none"> Added list of applicable HCPCS codes to reflect annual code edits: J2326 Archived previous policy version 2017D0059B
05/01/2017	Updated policy. Changed non-invasive ventilation criteria to clarify intent. Approved by National Pharmacy & Therapeutics Committee on 04/26/2017. Policy 2017D0059A archived.

Date	Action/Description
04/01/2017	New policy 2017D0059A. Approved by National Pharmacy & Therapeutics Committee on 01/25/2017.