

**POLICY:** Spinal Muscular Atrophy – Spinraza® (nusinersen injection for intrathecal use – Biogen)

**EFFECTIVE DATE:** 1/1/2020

**LAST REVISION DATE:** 11/01/2023

**COVERAGE CRITERIA FOR:** All UCare Plans

## OVERVIEW

Spinraza, a survival motor neuron 2 (SMN2)-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.<sup>1</sup>

### Disease Overview

Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder caused by deletion or loss of function mutation in the survival motor neuron 1 (SMN1) gene.<sup>2-5</sup> The reduced levels of survival motor neuron (SMN) protein causes degeneration of lower motor neurons.<sup>5</sup> Although the condition is a multisystem disorder, it is clinically characterized by progressive muscle weakness and atrophy. Patients have difficulties with ambulation, head control, feeding, and respiration. Cognitive development is not impacted. In the US, spinal muscular atrophy affects approximately one in 11,000 infants and has an average carrier frequency of one in 54 individuals; as many as 10,000 to 20,000 children and adults in the US may be impacted.<sup>5</sup> Although the condition can be present in individuals of any age, it is more frequently diagnosed in infants and children, as it is more severe in this population.<sup>2-5</sup> The phenotypic expression of the disease is impacted by the presence of the SMN2 gene copy number. SMN1 is responsible for producing most of the effective SMN protein, although some SMN protein can be made by the SMN2 gene. Therefore, patients with a deletion of the SMN1 gene may have the potential for making some SMN protein through the SMN2 gene copy, although in most cases the resulting protein made by this gene is truncated and is not as effective or functional. Data have shown that patients with a higher number of SMN2 copies generally have a more mild phenotypic disease expression. Gene deletion testing for spinal muscular atrophy can be performed at many diagnostic laboratories. Of note, various motor ability assessments are used in clinical practice to characterize functional impairment in spinal muscular atrophy.<sup>2-5</sup> A variety of functional motor scales are utilized to evaluate patients.<sup>6</sup> Table 1 describes disease types. A different manner of categorization classifies the three most common types as follows: Type 1 patients are “non-sitters”, Type 2 patients are “sitters”, and Type 3 patients are “walkers”.<sup>3,5</sup>

**Table 1. Types of Spinal Muscular Atrophy.**<sup>2-5</sup>

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Copy Gene Number
0	Prenatal	Severe hypotonia and weakness; respiratory failure at birth. There is no achievement of motor milestones.	A few weeks to < 6 months	0 to 1
1	< 6 months	Poor muscle tone, lack of movement, and respiratory assistance needed at birth. Patients are never able to sit.	< 2 years	1 to 2
2	Before 18 months	Patients are able to sit. However, patients are unable to walk or stand without assistance.	75% of patients are alive at 25 years of age	2 to 3
3	> 18 months	Walks independently but may lose this ability as the disease progresses.	Normal	3 to 4
4	Adulthood	Walk until adulthood.	Normal	≥ 4

SMA – Spinal muscular atrophy; SMN2 – Survival motor neuron 2.

Besides Spinraza, other therapies are available. **Evrysdi**<sup>®</sup> (risdiplam oral solution), a SMN2 splicing modifier, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.<sup>7</sup> The primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children and adults up to 25 years of age. Data are also available in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy.

**Zolgensma**<sup>®</sup> (onasemnogene abeparvovec-xioi intravenous infusion), an adeno-associated virus vector-based gene therapy, is indicated for the treatment of pediatric patients < 2 years of age with spinal muscular atrophy with bi-allelic mutations in the SMN1 gene.<sup>8</sup> The agent works by providing a copy of the gene encoding the SMN protein, which increases its production. Zolgensma is administered as a single-dose intravenous infusion over 60 minutes. Pivotal studies mainly involve infants with two or three SMN2 gene copies with primarily Type 1 or Type 2 disease.

### Clinical Efficacy

Spinraza was investigated in a pivotal trial called ENDEAR, which was a Phase III, multicenter, multinational, randomized, double-blind, sham-procedure controlled study involving 121 symptomatic infants diagnosed with infantile-onset spinal muscular atrophy (Type I).<sup>1,9</sup> Patients were randomized 2:1 to receive either Spinraza (n = 80) or sham injection (n = 41).<sup>1</sup> Eligible patients were ≤ 7 months of age at the time of the first dose and diagnosed with spinal muscular atrophy with a symptom onset prior to 6 months of age. Baseline demographics were balanced between the Spinraza and control groups with the exception of age at first treatment (median age of 175 and 206 days, respectively).<sup>1</sup> At baseline, all infants were symptomatic, hypotonic and weak, which are features consistent with a phenotype that is most likely to be categorized as spinal muscular atrophy Type 1.<sup>9</sup> Patients had two SMN2 gene copies. The median time of treatment was 261 days (range 6 to 442 days).<sup>1</sup> Those who received Spinraza compared with sham-control experienced improvement on achieving motor milestone responses. Outcomes assessing survival also revealed improvements for patients receiving Spinraza vs. sham control.

CHERISH was a multicenter, double-blind, sham-controlled, Phase III trial which involved children with symptomatic later-onset spinal muscular atrophy who were 2 to 12 years of age (n = 126) with likely Type 2 or 3 disease (symptom onset after 6 months of age).<sup>1,10</sup> Patients were randomized (2:1) to receive Spinraza or sham injection. Three SMN2 gene copies were reported among 88% of patients; approximately 8% of patients had two SMN2 gene copies. The median age at screening was 4 years and 3 years in the Spinraza and sham procedure control groups, respectively.<sup>1,10</sup> Patients who received Spinraza experienced more improvement in motor milestones compared with sham control.

NURTURE was an open-label uncontrolled trial involving patients with presymptomatic spinal muscular atrophy who ranged in age from 3 days to 42 days at the time of the first dose (n = 25).<sup>1,11</sup> Patients were required to have two or three SMN2 gene copies.<sup>11</sup> Some patients who were given Spinraza prior to the onset of symptoms related to spinal muscular atrophy survived without requiring permanent ventilation beyond what would be anticipated based on their SMN2 copy number. Also, some patients also met age-appropriate growth and development motor milestones (e.g., ability to sit unassisted, stand, or walk). Data are available from almost a median of 3-year follow-up.

The EMBRACE trial showed benefits of Spinraza in infants/children with infantile- or later-onset spinal muscular atrophy who were not eligible for the ENDEAR or CHERISH studies.<sup>12</sup> Other data with Spinraza are also available, including an accumulation of data in adults.<sup>13-26</sup> Follow-up is available for up to 4 years. Patients had a slowing of decline, achieved milestones, and experienced additional improvement in scales assessing motor function.

## Dosing

Spinraza is given intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.<sup>1</sup> The recommended dosage is 12 mg (5 mL) per administration. Initiate Spinraza treatment with four loading doses. The first three loading doses should be administered at 14-day intervals. The fourth loading dose should be given 30 days after the third dose. A maintenance dose should be given once every 4 months thereafter. There are additional recommendations in patients who have missed doses. The safety and effectiveness of Spinraza in pediatric patients from newborn to 17 years of age have been established.

## Guidelines

The Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group is comprised of clinicians and geneticists with expertise in spinal muscular atrophy who developed a treatment algorithm in 2018 for infants who have positive results from a newborn screening test for spinal muscular atrophy.<sup>27</sup> Spinal muscular atrophy Types 1 and 2 comprise a large majority of cases and account for many patients who screen positively for spinal muscular atrophy with three or fewer SMN2 gene copies. Immediate treatment is recommended in patients with two or three SMN2 gene copies. Treatment recommendations for patients who screen positive for spinal muscular atrophy and have only one SMN2 gene copy is more complicated.<sup>27</sup> In 2020, the Working Group updated recommendations that infants diagnosed with spinal muscular atrophy via newborn screening with four SMN2 gene copies should receive immediate treatment.<sup>28</sup> Also, patients with five (or more) SMN2 gene copies should be observed and screened for symptoms.

## POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Spinraza. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Due to the specialized skills required for evaluation and diagnosis of patients treated with Spinraza as well as the monitoring required for adverse events and long-term efficacy, approval requires Spinraza to be prescribed by a physician who has consulted with or who specializes in the condition. For certain criteria, verification is required as noted by **[verification in claims history required]**. All reviews will be forwarded by the Medical Director for evaluation.

**Documentation:** Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Spinal Muscular Atrophy – Spinraza Utilization Management Medical Policy* through the Coverage Review Department and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization except for the criterion requiring documentation of response or benefit to Spinraza therapy.

**Automation:** None.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Spinraza is recommended in those who meet the following criteria:

### **FDA-Approved Indications**

**1. Spinal Muscular Atrophy – Treatment.** Approve for the duration noted if the patient meets ONE of the following (A or B):

**A) Initial Therapy.** Approve for 6 months if the patients meets all of the following criteria (i, ii, iii, iv, v, vi and vii):

- i.** The medication is prescribed by or in consultation with a physician who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND
- ii.** Baseline motor ability assessment that suggest spinal muscular atrophy (based on age, motor ability, and development) is provided from one of the following exams (a, b, c, d, e, f, g or h)
  - a)** Bayley Scales of Infant and Toddler Development; OR
  - b)** Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); OR
  - c)** Hammersmith Functional Motor Scale Expanded (HFMSE); OR
  - d)** Hammersmith Infant Neurological Exam Part 2 (HINE-2); OR
  - e)** Motor Function Measure-32 Items (MFM-32); OR
  - f)** Revised Upper Limb Module (RULM) test; OR
  - g)** World Health Organization motor milestone scale; OR
  - h)** 6-minute walk test (6MWT); AND
- iii.** Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 (SMN1) gene **[documentation required]**; AND

Note: Pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations.

- iv.** The patient meets one of the following (a or b):
  - a)** If a pre-symptomatic infant, then  $\leq 3$  copies of SMN2 gene is required **[documentation required]**; OR
  - b)** If a symptomatic patient, then  $\geq 2$  copies of SMN2 gene is required **[documentation required]** and according to the prescriber has symptoms consistent with Types 1, 2, or 3 spinal muscular atrophy; AND
- v.** For a patient currently receiving or who has received prior treatment with Evrysdi<sup>®</sup> (risdiplam oral solution), the prescriber attests that further therapy with Evrysdi will be discontinued; AND
- vi.** The patient has not received Zolgensma<sup>®</sup> (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past; AND

Note: The prescriber must attest that the patient has not previously received Zolgensma.

**B) Patients Currently Receiving Spinraza Therapy.** Approve for 12 months if the patient meets all of the following criteria (i, ii, iii, and iv).

- i.** The medication is prescribed by or in consultation with a physician who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND
- ii.** Absence of toxicity from the drug including serious infections, glomerulonephritis, thrombocytopenia, etc; AND
- iii.** For a patient currently receiving or who has received prior treatment with Evrysdi<sup>®</sup> (risdiplam oral solution), the prescriber attests that further therapy with Evrysdi will be discontinued; AND
- iv.** The patient has not received Zolgensma<sup>®</sup> (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past; AND

Note: The prescriber must attest that the patient has not previously received Zolgensma.

- v. Patient has demonstrated improvement or lack of progression from baseline in at least one of the following **[documentation required]**.
  - a) Hammersmith Functional Motor Scale Expanded (HFMSE): at least 3 point increase from baseline
  - b) Hammersmith Infant Neurologic Exam (HINE): at least 2 point (or maximal score) increase in ability to kick OR at least 1 point increase in any other HINE milestone
  - c) 6-minute walk test (6MWT): increase of 30 meters if ambulatory
  - d) Upper limb module (ULM) score: at least 2 point increase from baseline
  - e) Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND): at least 4 point increase from baseline
  - f) Progression has been slower than otherwise would have been expected in this patient population

**Dosing.** Approve the following dosing regimens.

A) Initial Approval: Five 5mL (12mg/5mL) vials for the first 6 months

B) Renewal Approval: Three 5mL (12mg/5mL) vials for the subsequent 12 months

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### CONDITIONS NOT RECOMMENDED FOR APPROVAL

Spinraza has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. The patient is currently enrolled in clinical trials for Spinraza
2. The SMA without chromosome 5q mutations or deletions
3. SMA pre-symptomatic patients with > 3 copies of SMN2 gene
4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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**HISTORY**

Type of Revision	Summary of Changes	Date Reviewed
New Policy	Not applicable	08/15/2018
Update	5/24/2019: No criteria changes. The heading Spinal Muscular Atrophy was added to the policy title.	---
Annual revision	All Spinraza reviews will be done by the Medical Director. Changes below in criteria are described below. <b>1. Spinal Muscular Atrophy, Treatment:</b> The same criteria changes were made for patients who were receiving initial therapy and in patients currently receiving Spinraza Therapy. The notation of Type I, II, or III spinal muscular atrophy was removed. The criteria regarding the genetic test had the term “bi-allelic mutations” added. Criteria were added that the patient has two or three SMN2 gene copies (with documentation required) OR that the patient has four or more SMN2 gene copies (with documentation required) AND according to the prescribing physician the patient has symptoms consistent with Types 1, 2, or 3 spinal muscular atrophy. Criteria were added that the patient has not received Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past. It was added that the following laboratory tests will be evaluated prior to the administration of Spinraza: a) Prothrombin time and/or activated partial thromboplastin time; b) Platelet count; and c) Quantitative spot urine protein testing. <b>2. Conditions Not Recommended for Approval:</b> A criterion was added to not approve Spinraza if the patient has complete paralysis of limbs to suggest advanced	06/18/2019

	<p>spinal muscular atrophy. Additionally, a criterion was added to not approve Spinraza is the patient has permanent ventilator dependence to suggest advanced spinal muscular atrophy. In these clinical scenarios, data are needed to determine if this patient population would derive benefits from Spinraza.</p> <p><b>3. Initial Approval/Extended Approval:</b> This section was removed (no longer needed as the durations are incorporated into the criteria section).</p> <p><b>4. Duration of Therapy:</b> This section was removed (no longer needed as it is incorporated into the criteria section).</p> <p><b>5. Labs/Diagnostics:</b> This section was removed (no longer needed as it is incorporated into criteria).</p> <p><b>6. Waste Management:</b> This section was removed (no longer needed).</p>	
Selected revision	<p>“Prescriber” replaced the phrase “prescribing physician” in applicable places in the criteria. For patients currently receiving Spinraza therapy that was approved through a request from the ESI coverage review department, a note was added stating to provide an exception to the requirement of SMN2 gene copy information if, according to the prescriber, the patient has symptoms consistent with spinal muscular atrophy Types 1, 2 or 3.</p>	01/15/2020
Selected revision	<p>Approval for initial therapy was changed from 12 months to 3 months. The approval duration for patients currently receiving Spinraza therapy was changed from 12 months to one dose (for a dose to be used once within the next 4 months for maintenance therapy). For the criteria that requires that the patient has not received Zolgensma in the past, a note was added to verify through the claims history that the patient has not previously received Zolgensma and, if no claim for Zolgensma is present, the prescriber must attest that the patient has not previously received Zolgensma. For the requirement for patients who are currently receiving therapy that the patient has responded to Spinraza, a documentation requirement was added. Also, examples of response to therapy was moved from the criteria to a note.</p>	03/25/2020
Annual revision	No criteria changes.	06/03/2020
Selected Revision	Add criteria excluding concurrent use with Evrysdi	01/13/2021
Selected Revision	Removal of claims verification requirement for prior use with Zolgensma	04/26/2021
Early Annual Revision	<p><b>Spinal Muscular Atrophy – Treatment:</b> For initial therapy, criteria were added that a baseline motor ability assessment that suggests spinal muscular atrophy (based on age, motor ability, and development) is provided from one of the following exams with documentation required: Bayley Scales of Infant and Toddler Development, Third Edition (Item 22); Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; Hammersmith Functional Motor Scale Expanded; Hammersmith Infant Neurological Exam Part 2; Motor Function Measure-32 Items (MFM-32); Revised Upper Limb Module test; or the World Health Organization motor milestone scale. For a patient currently receiving Spinraza, criteria were more specific for a response to therapy by stating that the patient must have had a positive clinical response (for example, improvement or stabilization) from pretreatment baseline status (i.e., within the past 4 months) with Spinraza from one of the following, with documentation required: Bayley Scales of Infant and Toddler Development, Third Edition (Item 22); Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; Hammersmith Functional Motor Scale Expanded; Hammersmith Infant Neurological Exam Part 2; MFM-32; Revised Upper Limb Module test; or World Health Organization motor milestone scale OR meet the criteria regarding a response that was previously in place regarding use of physician monitoring/assessment tools, with examples still listed in a Note with continuation of documentation being required. Of note, many of the scales now specifically listed were provided in the previous examples that could be met regarding response to therapy. Updated to add 6-minute walk test (6MWT) to acceptable baseline motor ability assessments per MN DHS posted criteria. Removed documentation requirement as this is not a MN DHS requirement.</p>	10/19/2021
Annual Revision	No criteria changes.	10/05/2022
Selected Revision	Spinal Muscular Atrophy – Treatment: For both Initial Therapy and for a Patient Currently Receiving Spinraza Therapy, the reference to the Bayley Scales of Infant and Toddler	03/22/2023

	<p>Development had the descriptor of “Third Edition (BSID-III) [Item 22]” removed; this scale is still noted in criteria as an updated edition has been released. Previously, a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 gene reported as at least one of the following was required: homozygous deletion, homozygous mutation, or compound heterozygous mutation [documentation required]. This was revised to state that a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 gene [documentation required] is required with a Note added stating that pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations. The phrase “according to the prescriber” was removed from the requirement that the patient has objective signs consistent with spinal muscular atrophy Types 1, 2, and 3 since documentation is required. The criteria that state “prescriber” were changed to “prescribing physician”. The requirement of the following laboratory tests to be performed prior to administration of Spinraza were deleted: prothrombin time and/or activated partial thromboplastin time, platelet count, and quantitative spot urine protein testing. The phrase “verification in claims history required” replaced the previous wording of “verification required by prescriber”.                  Dosing: Recommendations were added regarding missed maintenance doses. Refer to the policy.</p>	
Annual Revision	No criteria changes per Care Continuum. No MN DHS updates since January 2020.	11/01/2023