

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

DATE REVIEWED: 06/03/2020

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.¹ Spinraza is an antisense oligonucleotide developed to treat spinal muscular atrophy caused by mutations in chromosome 5q which leads to survival motor neuron (SMN) protein deficiency. Spinraza has been demonstrated to increase exon 7 inclusion in SMN2 messenger ribonucleic acid transcripts and production of full-length SMN protein. Spinraza is given intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures. 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. The safety and effectiveness of Spinraza in pediatric patients from newborn to 17 years of age have been established.

Disease Overview

Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder that is clinically characterized by progressive muscle weakness and atrophy.^{2-7,21,22} It is more frequently diagnosed in infants and children and it is the most common genetic cause of death in infants. Proximal muscles (e.g., torso, legs, neck) are more impacted compared with distal muscles (e.g., hands, arms, feet). Patients with spinal muscular atrophy may never be able to, or progressively lose the ability to walk, stand, sit and/or ambulate. More severe disease manifests with poor head control (hypotonia), reduced reflexes, tongue movements and difficulties in swallowing and feeding. Respiratory illnesses and bone and/or spinal deformities may occur. However, cognitive development is not impacted. The incidence of spinal muscular atrophy is estimated to be 1 per 6,000 to 10,000 live births and is believed to impact as many as 10,000 to 25,000 children and adults in the US. Although it can vary among ethnic groups, the estimated carrier frequency ranges from 1 in 40 to 1 in 60 individuals; there are approximately 6 million carriers in the US. The disorder is caused by an abnormal or missing gene known as survival motor neuron 1 (SMN1), which is found on chromosome 5q (in band 13) and produces a protein essential to motor neurons. Devoid of this protein, lower motor neurons in the spinal cord do not function properly, can degenerate and die. The genetics of spinal muscular atrophy are complex. Most people have two nearly identical SMN genes, SMN1 and SMN2. There are also copies, sometimes multiple, of these two genes. SMN1 is responsible for producing most of the effective SMN protein, although some SMN protein is made by the SMN2 gene. Therefore, patients with a deletion of the SMN1 gene may have the potential for making some functional protein through the SMN2 gene, although in most cases the resulting SMN2 protein is truncated and is not as effective. The disease has a variable phenotypic expression due to the amount of the SMN protein produced, as well as due to backup copies of the gene. Data have shown that patients with a higher number of SMN2 copies generally have a more mild phenotypic disease expression. Diagnostic testing for spinal muscular atrophy can be performed at many laboratories.

Spinal muscular atrophy is generally divided into five different types, which differ in various aspects such as the age of onset, clinical severity, and life expectancy.³⁻⁵ Type 0 is the most severe form and progresses during pregnancy. Fetal movement may be reduced *in utero* and development is delayed. Respiratory distress occurs at birth, which may require a respirator, and death frequently occurs within weeks.³⁻⁵ Life expectancy is severely reduced as most patients are unable to survive beyond 6 months of

age.⁶ Type 1 generally occurs or manifests around or before the patient is 6 months of age. The symptoms are hallmarked by patients not being able to control head movement³⁻⁵ and profound hypotonia that manifests as a “froglike” posture when lying down.⁶ Developmentally, patients are unable to sit without assistance.³⁻⁵ Respiratory failure usually occurs before patients are 2 years of age.³⁻⁶ Type 2 disease has an onset between 6 to 18 months. Patients are generally able to sit independently; however, the ability to walk is usually not achieved without assistance.³⁻⁶ The lifespan is generally between 10 to 40 years.³⁻⁵ Type 3 typically manifests after the patient is 18 months of age or older.³⁻⁵ The main symptoms is progressive proximal weakness of the legs more than the arms.⁶ Some patients lose the ability to walk in adulthood whereas others may be able to walk without assistance throughout their normal lifespan.³⁻⁵ Type 4 is the mildest form of the disease. Symptoms of muscle weakness occur in adulthood (middle to late age) but patients usually retain the ability to walk. Lifespan is generally not reduced due to the disease. The incidence of the severe disease types (Type 0 and Type 1) is higher but due to the shortened lifespan, the prevalence is less; type 4 disease is not common. A different manner of categorization classifies the main three most common types as follows: Type 1 patients are “non-sitters”, Type 2 patients are “sitters”, and Type 3 patients are “walkers”. Table 1 displays the different disease classifications.

Table 1. Types of Spinal Muscular Atrophy.²⁻⁴

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Copy Gene Number
0	Prenatal	Minimal functioning, respirator required at birth.	< 6 months	0 to 1
1	< 6 months	Poor muscle tone, lack of movement, respiratory assistance needed. Patients are never able to sit.	< 2 years	1 to 3
2	6 to 18 months	Patients are able to sit. However, patients are unable to walk or stand without assistance.	10 to 40 years	2 to 3
3	> 18 months	Walks independently but may lose this ability as the disease progresses.	Adulthood	3 to 4
4	Adolescence to adulthood	Walk until adulthood.	Normal lifespan	≥ 4

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

Clinical Efficacy

Infantile-Onset Spinal Muscular Atrophy

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 spinal muscular atrophy (Type I).^{1,8} Patients were randomized 2:1 to receive either Spinraza (n = 80) or sham injection (n = 41).¹ 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. A planned interim efficacy analysis was performed based on patients who died, withdrew, or completed at least 183 days of treatment. 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).¹ 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 1.⁸ Patients had two SMN2 gene copies.

The primary endpoint assessed at the time of the interim analysis was the proportion of responders, defined as patients with improvement in motor milestones according to Section 2 of the Hammersmith Infant Neurologic Exam (HINE).¹ This endpoint assesses seven different areas of motor milestone development with a maximum score of 26. A treatment responder was defined as any patient with at least a 2-point increase (or maximal score of 4) in the ability to kick (consistent with improvement by at least

two milestones), or at least a 1-point increase in the motor milestones assessing head control, rolling, sitting, crawling, standing or walking (consistent with improvement by at least one milestone). The patient had to display improvement in more categories of motor milestones than worsening to be categorized as a responder. Although not statistically controlled for multiple comparisons at the interim analysis, the treatment effects on the Children’s Hospital of Philadelphia Test of Neuromuscular Disorders (CHOP-INTEND) were evaluated, which is also an assessment of motor skills in patients with infant-onset spinal muscular atrophy.¹

The median time of treatment was 261 days (range, 6 to 442 days).¹ Of the 82 patients deemed eligible for the interim analysis, a statistically significantly greater percentage of patients achieved a motor milestone response in the Spinraza group compared with sham-procedure control group (40% [n = 21/52] vs. 0% [n = 0/30], respectively).¹ On the final analysis, the proportion of patients categorized as motor milestone responders (HINE Section 2), were 51% for patients given Spinraza (n = 37/73) compared with 0% in the sham-control group (n = 0/37). Also, more patients given Spinraza vs. sham-procedure control on final analysis (71% [n = 52/73] vs. 3% [n = 1/37], respectively) achieved improvement from baseline of at least 4-points on the CHOP-INTEND, which assesses motor skills.¹ Additionally, in the final analysis, 22% of infants achieved full head control, 10% of infants were able to roll over, 8% of infants were able to sit independently who were given Spinraza; in the control group these milestones were not achieved by any infants. Event-free survival was also evaluated.^{1,8} The number of patients who died or received permanent ventilation was 39% (n = 31/80) for those given Spinraza compared with 68% of patients (n = 28/41) given placebo (P = 0.005). Overall survival was also improved with Spinraza therapy as the number of patients who died was 16% among those given Spinraza (n = 13/80) compared with 39% of patients (n = 16/41) in the sham-control group (P = 0.004).

Later-Onset Spinal Muscular Atrophy

CHERISH was a multicenter, double-blind, sham-controlled, Phase III trial which involved children with symptomatic 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).^{1,9} Patients were randomized (2:1) to receive four doses of Spinraza 12 mg intrathecally on Days 1, 29, 85, and 274 or sham procedure control. Patients had genetically-confirmed 5q spinal muscular atrophy.⁹ The trial took place at 24 sites in 10 countries and intended to have a treatment period of 9 months with a 6-month follow-up period. The primary endpoint was the change from baseline in the Hammersmith Functional Motor Scale Expanded (HFMSSE) total score at Month 15. Other secondary endpoints were assessed. The diagnosis occurred at a median age of 18 months. The median age at screening was 4 years and 3 years in the Spinraza and sham procedure control groups, respectively. Only approximately 18% of patients were able to walk with support and no patients were able to walk independently for greater or equal to 15 feet. Three SMN2 gene copies were reported among 88% of patients; approximately 8% of patients had two SMN2 gene copies. The baseline HFMSSE total score was 22.4 and 19.9 in the Spinraza and sham-procedure control groups, respectively. The treatment difference in change from baseline in HFMSSE score to Month 15 was highly clinically and statistically significant for patients given Spinraza (5.9 points [4.0 improvement with Spinraza vs. a -1.9 point decline for sham procedure control; P < 0.001]).⁹ In total, 57% of patients given Spinraza had an increase in the HFMSSE of at least three points vs. 26% of patients given sham-procedure control.^{1,9}

Presymptomatic Spinal Muscular Atrophy

Data from an open-label uncontrolled trial are available 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).¹ For study inclusion, patients were required to have two or three SMN2 gene copies.¹¹ Patients received Spinraza as a series of loading doses given intrathecally, followed by maintenance doses given once every 4 months. 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 3 year follow-up.¹¹

Other data with Spinraza are also available.¹²⁻¹⁹ SHINE evaluated patients with infantile-onset spinal muscular atrophy who were most likely to have Type 1 spinal muscular atrophy.¹² This involves longer-term data along patients who completed initial trial with Spinraza, as well as ENDEAR, CHERISH, or EMBRACE. Follow-up is available for up to 4 years. Patients experienced a reversal of decline and additional improvement in CHOP-INTEND scores over time with Spinraza therapy. Another analysis saw additional improvement with Spinraza in older children, most of whom has two or three SMN2 gene copies.¹³ ENDEAR evaluated patients who were not eligible for the pivotal ENDEAR or CHERISH studies, most of whom had two or three SMN2 gene copies.¹⁷ Patients experienced motor improvement. Data are accumulating in adults.^{10,17-20,23-27}

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.²⁰ Spinal muscular atrophy Types 1 and 2 comprise a large majority of spinal muscular atrophy cases and account for the majority of patients who screen positively for spinal muscular atrophy and have three or fewer SMN2 gene copies. The Working Group unanimously recommends immediate treatment for these patients to achieve a maximal response to treatment. The NURTURE trial with Spinraza that involved presymptomatic infants who had either two or three SMN2 gene copies supports this recommendation. Treatment recommendations for patients who screen positive for spinal muscular atrophy and have only one SMN2 gene copy or four or more SMN2 gene copies is more complicated. It is likely that patients with only one SMN2 gene copy will likely be symptomatic at birth and the physician should determine if treatment is warranted. The Committee reached consensus that patients with more than four SMN2 copies should not be treated immediately but screened carefully for symptom presentation.

Safety

The most common adverse events (AEs) with Spinraza in patients with infantile-onset spinal muscular atrophy were lower respiratory tract infection (55%) and constipation (35%). The most common AEs for patients with later-onset spinal muscular atrophy were pyrexia (43%), headache (29%), vomiting (29%), and back pain (25%). Spinraza has Warnings/Precautions regarding thrombocytopenia and coagulation abnormalities, as well as renal toxicity. Due to the increased risk of bleeding complications and renal toxicity, testing is required at baseline and prior to each dose. The following laboratory tests should be performed at baseline and prior to each Spinraza dose, and as clinically needed: platelet count; prothrombin time; activated partial thromboplastin time; and quantitative spot urine protein testing.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Spinraza. 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 or in consultation with a physician who specializes in the condition being treated. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Approvals are provided for the durations noted below. 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 and/or laboratory data. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Spinal Muscular Atrophy – Spinraza Policy* through the Coverage Review Department and who is requesting reauthorization, the criteria utilized do NOT require resubmission of documentation for reauthorization.

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 3 months if the patients meets all of the following criteria (i, ii, iii, iv and v):

- 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. The patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene reported as at least one of the following: homozygous deletion, homozygous mutation, or compound heterozygous mutation **[documentation required]**; AND
- iii. The patient meets one of the following (a or b):
 - a) The patient has two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR
 - b) The patient has four or more SMN2 gene copies **[documentation required]** and according to the prescriber has symptoms consistent with Types 1, 2, or 3 spinal muscular atrophy; AND
- iv. The patient has not received Zolgensma[®] (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past; AND
Note: Verify through 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.
- v. The following laboratory tests will be evaluated prior to the administration of Spinraza (a, b and c):
 - a) Prothrombin time and/or activated partial thromboplastin time; AND
 - b) Platelet count; AND
 - c) Quantitative spot urine protein test; OR

B) Patients Currently Receiving Spinraza Therapy. Approve for one dose (one dose to be used once within the next 4 months as maintenance therapy) if the patient meets all of the following criteria (i, ii, iii, iv, v and vi).

- 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. The patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene reported as at least

- one of the following (homozygous deletion, homozygous mutation, or compound heterozygous mutation **[documentation required]**); AND
- iii. The patient meets one of the following (a or b):
 - a) The patient two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR
 - b) The patient has four or more SMN2 gene copies **[documentation required]** and according to the prescriber has symptoms consistent with spinal muscular atrophy Types 1, 2, and 3; AND
Note: If the patient is currently receiving Spinraza that was approved through a request from the ESI coverage review department, an exception to the requirement of SMN2 gene copy information may be granted if, according to the prescriber, the patient has symptoms consistent with spinal muscular atrophy Types 1, 2, or 3.
 - iv. The patient has not received Zolgensma[®] (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past; AND
Note: Verify through 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.
 - v. The following laboratory tests will be evaluated prior to the administration of Spinraza (a, b and c):
 - a) Prothrombin time and/or activated partial thromboplastin time; AND
 - b) Platelet count; AND
 - c) Quantitative spot urine protein test; AND
 - vi. According to the prescriber, the patient has responded to Spinraza therapy **[documentation required]**.
Note: Examples of improvement, achievement, and/or maintenance in motor milestones should be demonstrated and can be evaluated by tests such as Hammersmith Infant Neurologic Exam (HINE) [section 2], Hammersmith Functional Motor Scale Expanded (HFMSE), Children’s Hospital of Philadelphia Test of Neuromuscular Disorders (CHOP-INTEND) [as well as other physician monitoring tools], pulmonary function tests showing improvement, reduced need for respiratory support, and/or prevention of permanent assisted ventilation.

Dosing. Approve the following dosing regimens.

- A) Initially give 12 mg given intrathecally as four loading doses of which the first three loading doses should be given at 14-day intervals and the fourth loading dose should be given 30 days after the third dose; AND/OR
- B) The maintenance dose is 12 mg intrathecally once every 4 months.

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 has complete paralysis of limbs to suggest advanced spinal muscular atrophy.** Data are needed to determine if this patient population would derive benefits from Spinraza.

2. **The patient has permanent ventilator dependence to suggest advanced spinal muscular atrophy.** Data are needed to determine if this patient population would derive benefits from Spinraza.
3. 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	<p>All Spinraza reviews will be done by the Medical Director. Changes below in criteria are described below.</p> <ol style="list-style-type: none"> 1. Spinal Muscular Atrophy, Treatment: 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. 2. Conditions Not Recommended for Approval: A criterion was added to not approve Spinraza if the patient has complete paralysis of limbs to suggest advanced spinal muscular atrophy. Additionally, a criterion was added to not approve Spinraza if 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. 3. Initial Approval/Extended Approval: This section was removed (no longer needed as the durations are incorporated into the criteria section). 4. Duration of Therapy: This section was removed (no longer needed as it is incorporated into the criteria section). 5. Labs/Diagnostics: This section was removed (no longer needed as it is incorporated into criteria). 6. Waste Management: This section was removed (no longer needed). 	06/18/2019
Selected revision	“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 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.	01/15/2020
Selected revision	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.	03/25/2020
Annual revision	No criteria changes.	06/03/2020

SMN2 – Survival motor neuron 2.