PRIOR AUTHORIZATION POLICY

POLICY: Spinal Muscular Atrophy – Spinraza Prior Authorization Policy
- Spinraza® (nusinersen intrathecal injection – Biogen)

REVIEW DATE: 10/05/2022

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]

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.[2-5] The reduced levels of survival motor neuron (SMN) protein causes degeneration of lower motor neurons.[5] 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.[5] 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.[2-5] The phenotypic expression of the disease is impacted by the presence of the survival motor neuron 2 (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.[2-5] Various functional motor scales are utilized.[6] 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".[3,5]

Table 1. Types of Spinal Muscular Atrophy.[2-5]

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®** (risdiplam oral solution), a SMN2 splicing modifier, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[7] 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® (onasemnogene abeparvovec-xioi suspension for 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.[8] 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).[1,9] 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.[9] Patients had two SMN2 gene copies. The median time of treatment was 261 days (range 6 to 442 days).[1] 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).[1,10] Patients were randomized (2:1) to receive Spinraza or sham injection. Patients had genetically-confirmed 5q spinal muscular atrophy.[10] 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.[1,10] 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).[1,11] For study inclusion, patients were required to have two or three SMN2 gene copies.[11] 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.[12] Other data with Spinraza are also available, including an accumulation of data in adults.[13-26] Follow-up is available for up to 4 years. Patients experienced a reversal 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.[1] 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.

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.[27] 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. 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.[27] 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.[28] Also, patients with five (or more) SMN2 gene copies should be observed and screened for symptoms.

Safety

Spinraza has Warnings/Precautions regarding thrombocytopenia and coagulation abnormalities, as well as renal toxicity.[1] 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 prescription benefit coverage of Spinraza. 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 or in consultation with a physician who specializes in the condition being treated. All reviews will be forwarded to 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 Prior Authorization 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. For certain criteria, verification is required as noted by **[verification required by prescriber]**. All reviews will be forwarded to the Medical Director for evaluation.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

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 patient meets all of the following criteria (i, ii, iii, iv, v, vi, and vii):
     - **i.** Baseline motor ability assessment that suggests spinal muscular atrophy (based on age, motor ability, and development) is provided from one of the following exams (a, b, c, d, e, f, or g) **[documentation required]**:
       - **a)** Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) [Item 22]; 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; AND
     - **ii.** 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.** Patient meets one of the following (a or b):
       - **a)** Patient has two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR
       - **b)** Patient meets both of the following criteria [(1) and (2)]:
         - **(1)** The patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND
         - **(2)** According to the prescriber, the patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND
     - **iv.** For a patient currently receiving or who has received prior treatment with Evrysdi® (risdiplam oral solution), the prescriber attests that further therapy with Evrysdi will be discontinued; AND
     - **v.** Patient has not received Zolgensma (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past **[verification required by prescriber]**; 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.
     - **vi.** 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 testing; AND
     - **vii.** Medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; OR
   - **B)** Patient Currently Receiving Spinraza Therapy. Approve for one dose (for a 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, vi, vii, and viii):

i. 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

ii. Patient meets one of the following (a or b):
- **a)** Patient has two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR
- **b)** Patient meets both of the following [(1) and (2)]:
  - **(1)** Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND
  - **(2)** According to the prescriber the patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND

iii. Four months has elapsed since the last dose; AND

iv. For a patient currently receiving or who has received prior treatment with Evrysdi (risdiplam oral solution), the prescriber attests that further therapy with Evrysdi will be discontinued; AND

v. Patient has not received Zolgensma (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past **[verification required by prescriber]**; AND
Note: Verify through claims 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.

vi. The following laboratory tests will be evaluated prior to 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 testing; AND

vii. Medication is prescribed a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND

viii. Patient must meet one of the following (a or b):
- **a)** 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 [(1), (2), (3), (4), (5), (6), or (7)] **[documentation required]**:
  - **(1)** Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) [Item 22]; OR
  - **(2)** Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); OR
  - **(3)** Hammersmith Functional Motor Scale Expanded (HFMSE); OR
  - **(4)** Hammersmith Infant Neurological Exam Part 2 (HINE-2); OR
  - **(5)** Motor Function Measure-32 Items (MFM-32); OR
  - **(6)** Revised Upper Limb Module (RULM) test; OR
  - **(7)** World Health Organization motor milestone scale; OR
- **b)** According to the prescriber, the patient has responded to Spinraza and continues to benefit from ongoing Spinraza therapy by the most recent (i.e., within the past 4 months) physician monitoring/assessment tools **[documentation required]**.
  Note: Examples include pulmonary function tests showing improvement, bulbar function test results suggest benefits, reduced need for respiratory support, decrease in the frequency of respiratory infections or complications and/or prevention of permanent assisted ventilation.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spinraza is not recommended in the following situations:

1. **Patient has Complete Paralysis of All Limbs.** Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Spinraza.

2. **Patient has Permanent Ventilator Dependence.** Data are needed to determine if this patient population with advanced spinal muscular atrophy 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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