UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Spinal Muscular Atrophy – Spinraza Utilization Management Medical Policy
- Spinraza® (nusinersen intrathecal injection – Biogen)

REVIEW DATE: 10/02/2024

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 SMN1 gene.[2-5] The reduced level of SMN protein causes degeneration of lower motor neurons. The phenotypic expression of the disease is impacted by the SMN2 gene copy number. 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. Table 1 describes the disease types. Of note, various motor ability assessments are used in clinical practice to characterize functional impairment in spinal muscular atrophy. Different functional motor scales are utilized to evaluate patients. When motor neuron function is lost, it cannot be regained, which greatly impacts patients who have experienced progression (e.g., patients with complete paralysis of limbs or permanent ventilator dependence).

Table 1. Types of Spinal Muscular Atrophy.[4]

	Age at Onset	Features/Clinical Presentation*	Lifespan*	SMN2 Gene Copy Number
Type 0 (< 1% of patients)	Birth	Severe hypotonia and weakness; respiratory failure at birth. There is no achievement of motor milestones. Patients will never be able to sit.	< 6 months	1
Type 1 (50% to 60% of patients)	< 6 months	Poor muscle tone, lack of movement, and respiratory assistance is needed. Patients are never able to sit.	< 2 years	1 to 2 for 80% of patients
Type 2 (30% of patients)	7 to 18 months	Patients are able to sit. However, patients are unable to walk or stand without assistance.	Close to normal	2 to 3 for 90% of patients
Type 3 (10% of patients)	18 months to 30 years	Walks independently but may lose this ability as the disease progresses.	Close to normal	3 to 5 for most patients
Type 4 (< 1% of patients)	> 18 years	Walk until adulthood.	Normal	4 for 75% of patients; 5 or 6 for 25% of patients

* Without disease-modifying treatment or mechanical ventilation; 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.[6] The primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular. Data are also available in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy.

Zolgensma® (onasemnogene abeparvovec-xioi intravenous infusion), an adeno-associated virus vector-based gene therapy, is indicated for the treatment of spinal muscular atrophy with bi-allelic mutations in the SMN1 gene in pediatric patients < 2 years of age.[7] 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).[1,8] 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. 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 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).[1,9] 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.[1,9] 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).[1,10] Patients were required to have two or three SMN2 gene copies.[10] 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.[11] Other data with Spinraza are also available, including an accumulation of data in adults.[12-25] 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.[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. 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.[26] 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.[26] 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.[27] 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. If claims history is available, verification is required in certain criteria as noted by **[verification in claims history required]**. 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 results, medical test results, claims records, prescription receipts, 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, are NOT required to re-submit 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 Indication

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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 (i, ii, iii, iv, v, and vi):
     - **i.** Baseline motor ability assessment that suggest spinal muscular atrophy (based on age, motor ability, and development) has been performed from ONE of the following exams (a, b, c, d, e, f, or g) **[documentation required]**:
       - **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; AND

ii. 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.

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 [(1) and (2)]:
(1) Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND
(2) 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 prescribing physician confirms that further therapy with Evrysdi will be discontinued; AND

v. Patient has not received Zolgensma (onasemnogene abeparvovec-xioi intravenous infusion) in the past **[verification in claims history required]**; AND
Note: If no claim for Zolgensma is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Zolgensma.

vi. 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 (one dose to be used once within the next 4 months as maintenance therapy) if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii).

i. 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.

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) 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 prescribing physician confirms 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 in claims history required]**; AND
Note: If no claim for Zolgensma is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Zolgensma.

vi. 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; AND

vii. 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; 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 prescribing physician, 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.

Dosing. Approve the following dosing regimens:

A) Initially give 12 mg 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; AND/OR

C) Missed maintenance doses must meet the following (i, ii, or iii):

i. At least 8 months but less than 16 months from the last dose: approve one 12 mg intrathecal dose to be given as soon as possible, followed by one additional dose 14 days later; OR
Note: Thereafter, the regular maintenance dose schedule should be followed.

ii. At least 16 months but less than 40 months from the last dose: approve the 12 mg intrathecal maintenance dose to be given as soon as possible, followed by two additional doses that must be given 14 days apart; OR
Note: Thereafter, the regular maintenance dose schedule should be followed.

iii. At least 40 months from the last dose. Dosing should be restarted as recommended in criterion A and B.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
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 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.	03/22/2023
Annual Revision	No criteria changes.	11/01/2023
Annual Revision	Regarding Documentation, medical test results and prescription receipts were added as examples; the example provided of laboratory "tests" was changed to laboratory "results". In the Policy Statement, regarding verification of claims history, the phrase "if claims history is available" was added to account for situations in which claims history is not present. **Spinal Muscular Atrophy – Treatment:** In criteria that the patient has not received Zolgensma in the past (with verification in claims history required), the Note was revised to account for situations in which a claims history is not available.	10/02/2024