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Nusinersen

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Overview

This policy supports medical necessity review for nusinersen (**Spinraza®**).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Nusinersen (Spinraza) is considered medically necessary when the following are met:

Spinal Muscular Atrophy (SMA) - Treatment. Individual meets **ALL** of the following criteria:

A. Onset of clinical signs and symptoms consistent with SMA occur at age 15 years or younger
B. Diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene confirmed by genetic testing, and reported as at least **ONE** of the following: homozygous deletion, homozygous mutation, or compound heterozygous mutation
C. Individual meets **ONE** of the following:

i. Has two or three survival motor neuron 2 (SMN2) gene copies
ii. Individual meets **BOTH** of the following criteria:
    a. Has four survival motor neuron 2 (SMN2) gene copies
    b. According to the prescriber, the individual has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3

D. Baseline motor ability assessment that suggests spinal muscular atrophy (based on age, motor ability, and development) is provided from **ONE** of the following exams:
    i. Bayley Scales of Infant and Toddler Development
    ii. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
    iii. Hammersmith Functional Motor Scale Expanded (HFMSE)
    iv. Hammersmith Infant Neurological Exam Part 2 (HINE-2)
    v. Motor Function Measure-32 Items (MFM-32)
    vi. Revised Upper Limb Module (RULM) Test
    vii. 6-Minute Walk Test (6MWT)
    viii. World Health Organization motor milestone scale
E. For individuals previously treated with Zolgensma, **BOTH** of the following criteria are met:
    i. At least 60 days have passed since Zolgensma administration
    ii. Documented clinical decline of minimally important clinical difference from pre-treatment baseline or highest post-treatment score achieved on **ONE** of the following motor exams:
        a. CHOP INTEND: Decline of at least 4 points
        b. HFMSE: Decline of at least 3 points
        c. HINE-2: Decline of at least 1 point
        d. RULM: Decline of at least 2 points
F. 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

Dosing. **ONE** of the following dosing regimens:
1. 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
2. The maintenance dose is 12 mg intrathecally once every 4 months
3. Missed maintenance doses must meet **ONE** of the following:
    i. At least 8 months but less than 16 months from the last dose: one 12 mg intrathecal dose to be given as soon as possible, followed by one additional dose 14 days later
    Thereafter, the regular maintenance dose schedule should be followed
    ii. At least 16 months but less than 40 months from the last dose: 12 mg intrathecal maintenance dose to be given as soon as possible, followed by two additional doses that must be given 14 days apart
    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 1 and 2.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of nusinersen (Spinraza) is considered medically necessary for the treatment of spinal muscular atrophy when **ALL** of the following are met:
1. The above medical necessity criteria have been met prior to the start of Spinraza

2. There is documentation of a positive clinical response (for example, improvement or stabilization) since initiating Spinraza compared with pretreatment baseline status as evidenced by **ONE** of the following exams, or prescriber monitoring/assessment tools (based on age and motor ability), in the last 4 months
   A. Bayley Scales of Infant and Toddler Development
   B. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
   C. Hammersmith Infant Neurological Exam Part 2 (HINE-2)
   D. Hammersmith Functional Motor Scale Expanded (HFMSE)
   E. Motor Function Measure-32 Items (MFM-32)
   F. Revised Upper Limb Module (RULM) Test
   G. 6-Minute Walk Test (6MWT)
   H. World Health Organization motor milestone scale
   I. Physician monitoring tools (pulmonary function test, bulbar function, and/or reduced need for respiratory support)

Authorization Duration

Initial approval duration: up to 6 months.
Reauthorization approval duration: up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven including the following (this list may not be all inclusive):

1. **Individual 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. **Individual has Permanent Ventilator Dependence.**
   Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Spinraza.

   Permanent Ventilator Dependence is defined as tracheostomy or ventilatory support for at least 16 hours per day for more than 21 continuous days in the absence of an acute reversible event.

3. **Concurrent use of risdiplam (Evrysdi).**

Coding / Billing Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
96450	Chemotherapy administration, into CNS (e.g., intrathecal), requiring and including spinal puncture

HCPCS Codes	Description
J2326	Injection, nusinersen, 0.1 mg

Background

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 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] A variety of functional motor scales are utilized to evaluate patients.[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 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. 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. 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] 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 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.[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.[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.

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