Spinraza (nusinersen)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Spinraza policy is to encourage appropriate use according to clinical guidelines and/or clinical trials in the treatment of spinal muscular atrophy (SMA).

Spinraza (nusinersen) is an intrathecally administered antisense oligonucleotide that increases the amount of functional survival motor neuron (SMN) protein which is deficient in individuals diagnosed with SMA. SMA is a rare, and often fatal, genetic disease affecting muscle strength and movement.

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the patient has no exclusions to the prescribed therapy.

FDA-Approved Indications

Spinraza is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

POLICY

Required Documentation

The following information is necessary to initiate the prior authorization review:

I. Initiation of therapy:
- Deletion or mutation at the SMN1 allele confirmed by genetic testing.
- Medical records (e.g., chart notes, laboratory values) of the baseline assessment for at least one of the following assessment tools (based on patient age and motor ability) to establish baseline motor ability:
  - Hammersmith Infant Neurological Exam Part 2 (HINE-2)

- Hammersmith Functional Motor Scale Expanded (HFMSE)
- Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)

- Medical records documenting respiratory status and need for respiratory support

II. Continuation of therapy:

- Medical records (e.g., chart notes, laboratory values) of the most recent (less than 1 month prior to continuation request) assessment by at least one of the following assessments:
  - HINE-2
  - HFMSE
  - CHOP-INTEND
  - For patients prescribed Spinraza due to clinical worsening after receiving gene therapy: Documentation of the impact of Spinraza therapy (e.g., impact on motor milestones)

Criteria for Initial Approval

I. Spinraza (nusinersen) may be considered **medically necessary** for the treatment of spinal muscular atrophy (SMA) in patients who meet the following criteria:

- Patient has a diagnosis of SMA confirmed by genetic testing showing deletion or mutation at the SMN1 allele (examples below)
  - Homozygous gene deletion or mutation (e.g., homozygous deletion of exon 7 at locus 5q13)1,5; or
  - Compound heterozygous mutation (e.g., deletion of SMN1 exon 7[allele 1] and mutation of SMN1 [allele 2])
- Patient has Type 1, Type 2 or Type 3 SMA
- The diagnosis was made at or before 18 years of age
- The medication must be prescribed by or in consultation with a neurologist or neuromuscular specialist with expertise in the treatment of SMA
- Patient is not dependent on either of the following:
  - Invasive ventilation or tracheostomy
  - Use of non-invasive ventilation beyond use for naps and nighttime sleep
- One of the following criteria is met:
  - Patient has not previously received gene therapy for SMA, or
  - Patient has previously received gene therapy for SMA and has experienced a decline in clinical status that demonstrates a loss of efficacy of the gene therapy as demonstrated by a decline of minimally clinical important difference from highest score achieved on one of the following exams (based on patient age and motor ability):
    - HINE-2: Decline of at least 2 points on kicking and 1 point on any other milestone (excluding voluntary grasp)
    - HFMSE: Decline of at least 3 points
    - CHOP-INTEND: Decline of at least 4 points
- Patient will not use Spinraza and Evrysdi (risdiplam) concomitantly
- If the patient has not received a loading dose, the loading dose will be dosed at 12 mg (5mL) on Day 0, 14, 28, and 58.

Initial **Approval** will be for 6 months.

II. Spinraza (nusinersen) is considered **investigational** for the following:

- Use of Spinraza (nusinersen) in patients with type 0 and 4 spinal muscular atrophy (SMA)
- Use of Spinraza (nusinersen) in patients with type 1,2, and 3 spinal muscular atrophy (SMA) who require permanent ventilation
- Concomitant use of Spinraza (nusinersen) and gene therapy
- Concomitant use of Spinraza (nusinersen) and Evrysdi (risdiplam)

Continuation of Therapy

Note: Patients who were previously established on Spinraza and subsequently administered gene therapy must meet all initial criteria prior to re-starting therapy on Spinraza.

I. For continuation therapy, Spinraza (nusinersen) may be considered **medically necessary** for the treatment of spinal muscular atrophy (SMA) in patients who meet the initial criteria above and one of the following criteria:
   - Patient has type 1, type 2 or type 3 SMA.
   - Patient is not dependent on either of the following:
     - Invasive ventilation or tracheostomy
     - Use of non-invasive ventilation beyond naps and nighttime sleep
   - Submission of medical records (e.g., chart notes, laboratory values) of the most recent (less than 1 month prior to continuation request) assessment documenting a positive clinical response from pretreatment baseline to Spinraza therapy, as demonstrated by at least one of the following assessments:
     - HINE-2
       - One of the following:
         - Patient exhibited improvement or maintenance of previous improvement of at least a 2 point (or maximal score) increase in ability to kick; or
         - Patient exhibited improvement or maintenance of previous improvement of at least a 1 point (or maximal score) increase in any other HINE-2 milestone (e.g., head control, rolling, sitting, crawling, standing, or walking) excluding voluntary grasp; and
       - One of the following:
         - Patient exhibited improvement or maintenance of previous improvement in more HINE-2 motor milestones than worsening (net positive improvement); or
         - Patient achieved and maintained any new motor milestones when they would otherwise be unexpected to do so (e.g., sit or stand unassisted, walk)
     - HFMSE
       - One of the following:
         - Patient exhibited improvement or maintenance of previous improvement of at least a 3-point increase in score; or
         - Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so
     - CHOP-INTEND
       - One of the following:
         - Patient exhibited improvement or maintenance of previous improvement of at least a 4-point increase in score; or
         - Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so
     - The patient was prescribed Spinraza due to clinical worsening after receiving gene replacement therapy and there is documentation of stabilization or improvement in clinical status with Spinraza therapy (e.g. impact on motor milestones).
   - If patient has already received a loading dose, the maintenance dose will not exceed 12 mg (5 mL) every 4 months.

Approval will be for 12 months

*Note: If an individual meets medically necessary criteria, dosing of nusinersen treatment is covered according to the Food and Drug Administration (FDA) product information label. The FDA recommends that a maintenance dose should be administered once every 4 months. As noted above, to continue therapy,

medically necessary criteria requires the evaluation and demonstration of nusinersen's clinical effectiveness in the treated individual every 12 months.

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

CLINICAL RATIONALE

Infantile-Onset or Type I SMA

For individuals who have type I (infantile-onset) SMA who receive nusinersen, the evidence includes two randomized, double-blind, controlled trial (results not yet reported for one) and a single-arm open-label study. The relevant outcomes are OS, change in disease status, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. The largest phase 3 confirmatory, Assess the Efficacy and Safety of Nusinersen in Infants with SMA trial (n=121) showed clinically meaningful and statistically significant improvement in motor milestones, event-free survival, and OS that exceeded those seen in the control group, with an acceptable safety profile. The proportion of patients, who met the primary endpoint responder definition of achieving motor milestones, was 51% in the nusinersen arm compared with 0% in the sham-controlled arm. Further, the hazard ratio for event-free survival was 0.53 favoring nusinersen over sham-controlled. It is notable, however, that 50% of nusinersen-treated subjects did not achieve the primary endpoint motor milestone response. Only a small proportion of patients (6%) gained the ability to sit without assistance. On average, the mean motor milestone score in nusinersentreated patients improved by three points over six months. Given the limited data on the durability of response, long-term safety, and lack of efficacy in a substantial number of patients continued risk-benefit assessment of long-term treatment with nusinersen is necessary. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Type II and III SMA

For individuals who have type II or III SMA who receive nusinersen, the evidence includes four single-arm studies and a double-blind, randomized controlled trial. The relevant outcomes are OS, change in disease status, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. Efficacy findings from single-arm studies of type II and III SMA are difficult to interpret because these trials used a wide range of nusinersen doses and lacked control arms. The largest phase 3 confirmatory, Assess Clinical Efficacy and Safety of Nusinersen in Participants with Later-onset SMA trial (n=126) showed clinically meaningful and statistically significant improvement in motor milestones (measured using Hammersmith Functional Motor Scale–Expanded scores) that exceeded those seen in the control group (difference of 5.9 points favoring nusinersen over sham control, $p<0.001$). The respective proportion of patients with clinically meaningful improvements in Hammersmith scores greater than 3 points was 57% vs 26% ($p<0.001$). Multiple secondary endpoints also showed a consistency in treatment effect favoring nusinersen over sham control. Given the limited data on the durability of response, long-term safety, and lack of efficacy in a substantial number of patients continued risk-benefit assessment of long-term treatment with nusinersen is necessary. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Type 0 and IV SMA

For individuals who have Type 0 or IV SMA who receive Spinraza (nusinersen), the evidence is lacking. The relevant outcomes are a change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and treatment-related morbidity. The evidence is insufficient to determine the effects of technology on health outcomes.

Type I, II, and III SMA with permanent ventilation

Clinical studies have shown that Spinraza reduces the risk of permanent ventilation (defined as tracheostomy or 16 or more hours of ventilator support per day continuously for at least 2 weeks in the absence of an acute reversible illness); however, Spinraza has not been studied in patients who already require permanent ventilation in any sub-type of SMA. Subsequently, Wellmark's Medical Policy considers Spinraza investigational in patients who already require permanent ventilation due to the lack of evidence demonstrating Spinraza will be safe and effective in those patients.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD Diagnostic Codes.

- J2326, Spinraza Inj (nusinersen) 0.1mg

REFERENCES

- Spinraza [package insert]. Cambridge, MA: Biogen Inc; June 2019.
- Arnold WD, Kassar D, Kissel JT, et al. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle & Nerve. 2015;51(2):157-167.
- Burgunder JM, Schols L, Baets J, et al. EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders. European J Neurol. 2011;18:207-217.
- Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet. 2016;388:3017-26.
- Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med*. 2017; 377:1723-1732.
- Ionis Pharmaceuticals, Inc. A Study to Assess the Efficacy and Safety of IONIS-SMN Rx in Infants with Spinal Muscular Atrophy. In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (US). 2000- [2016 Feb 14]. Available from: https://clinicaltrials.gov/ct2/show/NCT02193074.
- Ionis Pharmaceuticals, Inc. A Study to Assess the Efficacy and Safety of IONIS-SMN Rx in Patients with Later-onset Spinal Muscular Atrophy. In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (US). 2000- [2016 Feb 14]. Available from: https://clinicaltrials.gov/ct2/show/NCT02292537.
- Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med*. 2018; 378:625-635.
- Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard care in spinal muscular atrophy. J Child Neurol. 2007;22(8):1027-1049.
- BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.28, 6/24/2019
- Zolgensma [package insert]. Bannockburn, IL. AveXis, Inc; May 2019.
- Institute for Clinical and Economic Review (ICER). Spinraza® and Zolgensma® for Spinal for Spinal Muscular Atrophy: Effectiveness and Value. Final Evidence Report April 3, 2019 (Updated May 24, 2019). 2019. Available at: https://icer-review.org/wpcontent/uploads/2018/07/ICER_SMA_Final_Evidence_Report_052419.pdf.Last accessed June 2019.
- Wadman RI et al. Drug Treatment for Spinal Muscular Atrophy Types II and III. *Cochrane Database Syst Rev*. 2020;1(1):CD006282.
- Darras BT et al. Nusinersen in Later-Onset Spinal Muscular Atrophy: Long-term Results From the Phase 1/2 Studies. *Neurology*. 2019;92(21):e2492-e2506.
- Curesma. Best Practices for Physical Therapists & Clinical Evaluators in Spinal Muscular Atrophy (SMA): Recommendations to Support the Effective Conduct of Clinical Trials in SMA. Available at: https://www.curesma.org/wp-content/uploads/2019/11/Cure-SMA-Best-Practices-for-PTs-and-CE-in-SMA-Clinical-Trials-Nov-2019.pdf. Accessed June 2020.

- De Vivo et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. *Neuromuscular Disorders*. 2019:842-856.
- Meylemans A, De Bleecker J. Current Evidence for Treatment With Nusinersen for Spinal Muscular Atrophy: A Systematic Review. *Acta Neurol Belg*. 2019;119(4):523-533.

*Some content reprinted from CVSHealth

POLICY HISTORY

Policy #: 05.02.05
Policy Creation: March 2017
Reviewed: October 2020
Revised: August 2020
Current Effective Date: October 2, 2020