Clinical Policy: Nusinersen (Spinraza)

Reference Number: PA.CP.PHAR.327
Effective Date: 01/2018
Last Review Date: 01/2025

Description
Nusinersen (Spinraza™) is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide.

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

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Spinraza is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Spinal Muscular Atrophy (must meet all)**:**

1. Diagnosis of SMA;
2. Genetic testing confirming 1, 2, 3, or 4 copies of SMN2 gene;
3. Genetic testing confirms the presence of one of the following (a, b or c):
   a. Homozygous deletions of SMN1 gene (e.g., absence of the SMN1 gene);
   b. Homozygous mutation in the SMN1 gene (e.g., biallelic mutations of exon 7);
   c. Compound heterozygous mutation in the SMN1 gene (e.g., deletion of SMN1 exon 7 (allele 1) and mutation of SMN1 (allele 2));
4. Prescribed by or in consultation with a neurologist;
5. Documentation of one of the following baseline scores (*see Appendix D*) (a or b):
   a. For age < 2 years: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder (CHOP-INTEND) score or Hammersmith Infant Neurological Examination (HINE) Section 2 motor milestone score;
   b. For age ≥ 2 years: Hammersmith functional motor scale expanded (HFMSE) score; Revised Hammersmith Scale (RHS), Upper Limb Module (ULM), Revised Upper Limb Module (RULM), or 6-Minute Walk Test (6MWT); Spinraza is not being initiated simultaneously with Evrysdi or Zolgensma®;
6. Spinraza is not prescribed concurrently with Evrysdi;
7. If the member is currently on Evrysdi, documentation of prescriber attestation of Evrysdi discontinuation upon initiation of Spinraza;
8. If the member has a history of treatment with Zolgensma, must meet the following (a and b):
   a. Provider must submit evidence of poor response to Zolgensma (e.g., sustained decrease in CHOP-INTEND score over a period 6 months);
   b. Documentation of provider attestation of clinical deterioration;
9. Dose does not exceed 12 mg per dose, prescribed for intrathecal use.

Approval duration: 12 months (up to 6 doses)

B. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Therapy

A. Spinal Muscular Atrophy (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy (PA.PHARM.01) applies;
2. Provider submits documentation of the number of categories of improvement and decline in motor milestones based on the CHOP-INTEND, HINE, or HFMSE score (based on member's age) since the most recent approval (*see Appendix D*);
3. Spinraza is not prescribed concurrently with Evrysdi and/or Zolgensma;
4. If request is for a dose increase, new dose does not exceed 12 mg every 4 months prescribed for intrathecal use.

Approval duration: 12 months

B. Other diagnoses/indications (1 or 2):

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to PA.CP.PMN.53

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder
FDA: Food and Drug Administration
HFMSE: Hammersmith functional motor scale expanded
HINE: Hammersmith Infant Neurological Examination
RHS: Revised Hammersmith Scale
RULM: Revised Upper Limb Module
SMA: spinal muscular atrophy
SMN: survival motor neuron
ULM: Upper Limb Module
6MWT: 6-Minute Walk Test

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Evrysdi® (risdiplam)	Weight-based dose PO QD: • Less than 2 months of age: 0.15 mg/kg • 2 months to less than 2 years of age: 0.2 mg/kg • 2 years of age and older, weighing less than 20 kg: 0.25 mg/kg	5 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	• 2 years of age and older, weigh 20 kg or more: 5 mg	

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- SMA is an autosomal recessive genetic disorder. It is caused by mutations in the SMN1 (survival motor neuron) gene that is found on chromosome 5 (hence the name 5q-SMA). To develop SMA, an individual must inherit two faulty (deletion or mutation) SMN1 genes, one from each parent.
- There are other types of SMA that are not related to chromosome 5 or SMN. Safety and efficacy of Spinraza in non-SMN-related SMA have not been established.
- SMN-related SMA is classified as type 1 through 4 depending on time of onset. The age of disease onset of symptoms correlates with disease severity: the earlier the age of onset, the greater the impact on motor function. Children who display symptoms at birth or in infancy typically have the lowest level of functioning (type 1). SMA onset in children (types 2 and 3), teens or adults (type 4) generally correlates with increasingly higher levels of motor function.
- Efficacy of Spinraza was established primarily in infantile disease (SMA type 1). Spinraza was approved based on interim results of an unpublished Phase III study of patients with spinal muscular atrophy type I (infantile-onset). The phase III study, referred to as ENDEAR, enrolled infants diagnosed with symptomatic, genetically confirmed spinal muscular atrophy (SMA) type I with two copies of SMN2 gene. Key inclusion criteria were: genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation or compound heterozygote, onset of clinical signs and symptoms consistent with SMA at ≤ 6 months, at study entry, receiving adequate nutrition and hydration) with or without gastrostomy), seven month of age or younger at screening, body weight ≥ 3rd percentile for age, gestational age of 37 to 42 weeks. Key exclusion criteria were: Hypoxemia and signs or symptoms of SMA present at birth within the 1st week after birth
- Based on the mechanism of action of Spinraza, SMN2 must be present in sufficient amount for the production of full length SMN protein required to alleviate or minimize the symptoms of SMA.
- All subjects in the ENDEAR study had at least 2 copies of SMN2 genes (98% of the subjects in the pivotal study had 2 copies of SMN2 genes, while other had 3 or 4 copies).
- It is unknown whether patients with less than 2 copies would make sufficient SMN protein to mitigate the symptoms of SMA as the efficacy of this agent has not been demonstrated in patients with less than 2 copies of SMN 2 genes.
- SMN2 gene copy and SMA types
  - SMN2 gene copy numbers are variable in individuals with spinal muscular atrophy. Higher numbers typically correlate with less severe disease.

  - More than 95% of individuals with spinal muscular atrophy retain at least 1 copy of the SMN2 gene
  - About 80% of individuals with Type I spinal muscular atrophy have 1 or 2 copies of the SMN2 gene
  - About 82% of individuals with Type II spinal muscular atrophy have 3 copies of the SMN2 gene
  - About 96% of individuals with Type III spinal muscular atrophy have 3 or 4 copies of the SMN2 gene
- The CHOP-INTEND score is a validated 16-item, 64-point scale shown to be reliable and sensitive to change over time for SMA Type 1. In a prospective cohort study of SMA type I patients (n = 34), the mean rate of decline in the CHOP-INTEND score was 1.27 points/year (95% CI 0.21-2.33, p = 0.02).
- The HINE Section 2 motor milestone exam is an easily performed and relatively brief standardized clinical neurological examination that is optimal for infants aged between 2 and 24 months with good inter-observer reliability. This endpoint evaluates seven different areas of motor milestone development, with a maximum score between 2-4 points for each, depending on the milestone, and a total maximum score of 26 points.
- The HFSME score combines the Hammersmith Functional Motor Scale with a 13-item expansion module for ability to distinguish motor skills among individuals who may be older or with SMA types II and III. Each item is graded from 0 to 3, with 0 signifying no response, with a total of 66 points.
- The RHS is an ordinal scale which consist of 33 items with grades of 0,1 and 2. For individuals who can achieve the task without any compensation it is given a score of 2. For those who only attempt the movement or finish it with some form of compensation is scored 1 and sore of 0 is given when patients are unable to perform any part of the item. The total maximum score is 69 points.
- The RULM is a set of 19 tasks that measure motor function in non-ambulatory SMA patients. Each task is assessed with a 3 point ordinal scale, with a total maximum score of 37 points. Meanwhile, the maximum score for ULM was 18.
- The 6MWT is a clinical outcome measure for ambulatory SMA that has been determined to be functionally meaningful and capable of capturing disease severity.

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
SMA	**Initial** (4 loading doses): 12 mg intrathecally every 14 days for 3 doses (loading doses); then, a fourth loading dose of 12 mg intrathecally 30 days after the third loading dose **Maintenance**: 12 mg intrathecally every 4 months	12 mg intrathecally every 4 months

V. Product Availability

Solution for intrathecal injection: 12 mg/5 mL

VI. References

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7. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med 2018; 378:625-35. DOI: 0.1056/NEJMoa1710504
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Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J2326	Injection, nusinersen, 0.1 mg

Reviews, Revisions, and Approvals	Date
Updated specialist requirement to pediatric neurologist. Added HFMSE baseline score for age >2 yo. Expanded indication to SMA types 1-3 with SMN2 copies up to 4. References reviewed and updated	02/2018
1Q 2019 annual review: references reviewed and updated.	01/2019
1Q 2020 annual review: removed requirement for documentation of number of categories of improvement for continued approval; added criteria preventing concurrent prescribing of Zolgensma; added criteria requiring medical justification, attestation, and evidence of clinical deterioration in members with a history of Zolgensma administration; added that member does not have respiratory insufficiency; Changed initial approval duration from 6 months to 12 months and added quantity limit of 4 doses to allow for interruptions in administration of initial loading doses while still requiring an evaluation prior to transition into maintenance therapy; references reviewed and updated.	01/2020
1Q 2021 annual review: references reviewed and updated.	01/2021
1Q 2022 annual review: Updated criteria language to restrict concomitant use with Evrysdi; Amended initial criteria to include validated functional tests: RHS, ULM, RULM, 6MWT for age ≥ 2 years; references reviewed and updated.	01/2022
1Q 2023 annual review: updated continuation criteria for response to therapy; updated appendix B dosing due to pediatric extension of Evrysdi; references reviewed and updated.	01/2023
1Q 2024 annual review: no significant changes; references reviewed and updated.	01/2024
1Q 2025 annual review: no significant changes; references reviewed and updated.	01/2025