

Clinical Policy: Nusinersen (Spinraza)

Reference Number: PA.CP.PHAR.327

Effective Date: 01/18

Last Review Date: 01/19

[Coding Implications](#)

[Revision Log](#)

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

It is the policy of health plans affiliated with Pennsylvania Health and 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 spinal muscular atrophy (SMA) Types I, II, or III;
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 pediatric 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;
6. Total dose does not exceed 4 doses of 12 mg, prescribed for intrathecal use.

Approval duration: 6 months

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 Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.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. If request is for a dose increase, new dose does not exceed 12 mg every 4 months prescribed for intrathecal use.
4. Member is receiving a clinical benefit based on the prescriber's assessment.

Approval duration: 12 months

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

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

Background

Description/Mechanism of Action:

Spinraza is an antisense oligonucleotide designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Using in vitro assays and studies in transgenic animal models of SMA, Spinraza was shown to increase exon 7 inclusion in SMN2 messenger ribonucleic acid transcripts and production of full-length SMN protein.

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
SMA: spinal muscular atrophy
SMN: survival motor neuron

Appendix B: Therapeutic Alternatives

Not applicable

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 $\geq 3^{\text{rd}}$ 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.

IV. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|------------|---|------------------------------------|
| SMA | <p>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</p> <p>Maintenance: 12 mg intrathecally every 4 months</p> | 12 mg intrathecally every 4 months |

V. Product Availability

Solution for intrathecal injection: 12 mg/5 mL

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.

| HCPSC Codes | Description |
|-------------|-------------|
| N/A | |

| Reviews, Revisions, and Approvals | Date | Approval 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 | 02/18 | |
| 1Q 2019 annual review: references reviewed and updated. | 01/19 | |

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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