Clinical Policy: Nusinersen (Spinraza)

Reference Number: CP.PHAR.327
Effective Date: 11.28.17
Last Review Date: 02.19 Coding Implications
Line of Business: Commercial, Medicaid, HIM-Medical Benefit Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 health plans affiliated with Centene Corporation® 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 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 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

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is

NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member meets one of the following based on age (a or b):
   a. For age < 2 years: maintenance or improvement in the CHOP-INTEND or HINE motor milestone score since the most recent approval;
   b. For age ≥ 2 years, one of the following (i or ii):
      i. If first renewal since turning 2 years old: maintenance or improvement in the CHOP-INTEND or HINE motor milestone score since the most recent approval AND submission of baseline HFMSE score (*see Appendix D*);
      ii. If > 2 years at therapy initiation or subsequent renewal since turning 2: maintenance or improvement in the HFMSE score 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.

Approval duration: 12 months

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial and CP.PMN.53 for Medicaid and HIM-Medical Benefit or evidence of coverage documents.

IV. 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 ≥ 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.

V. 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

VI. Product Availability

Solution for intrathecal injection: 12 mg/5 mL

VII. References

1. Spinraza Prescribing Information. Cambridge, MA: Biogen Inc.; October 2018. Available at: https://www.spinraza-hcp.com/. Accessed November 2, 2018.
2. Wang CH, Finkel RS, Bertini ES, et al. Consensus Statement for Standard of Care in Spinal Muscular Atrophy. Journal of Child Neurology 2007; 22:1027-1049.
3. Cobben JM, de Visser M, Scheffer H, et al. Confirmation of clinical diagnosis in requests for prenatal prediction of SMA type I. J Neurol Neurosurg Psychiatry 1993; 56: 319-21.
4. Maitre NL, Chorna O, Romeo DM, and Guzzetta A. Implementation of the Hammersmith Infant Neurological Examination in a High-Risk Infant Follow-Up Program. Pediatric Neurology 2016; 65:31-38.
5. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med 2017; 377:1723-32. DOI: 10.1056/NEJMoa1702752
6. Finkel RS, Chiriboga CA, Day JW, et al. Treatment of Infatile-Onset Spinal Muscular Atrophy with Nusinersen: A Phase 2, Open-Label, Dose-Escalation Study. The Lancet 2016;16:31408-8.

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
8. Darras BT, Royden Jones H Jr, Ryan MM, et al. Neuromuscular Disorders of Infancy, Childhood, and Adolescence: A Clinician's Approach. 2nd ed. London, UK: Elsevier; 2015.
9. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology 2014; 83:810-817.

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
C9489	Injection, nusinersen, 0.1 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	01.17	02.17
Initial approval criteria: added three or four copies of SMN2	01.24.17	02.15.17
Revisions: Initial criteria: Updated # of copies of SMN2 from 3,4,or 5 to 1 or 2 copies Changed diagnosis of SMA type I to sxs of SMA before 6 months of age Removed criterion for SMA type IV Updated specialist requirement to pediatric neurologist Added HFMSE baseline score for age >2 yo Continuation criteria: Specifically divided up positive response to tx via HINE or HFMSE score based on age Added requirement of number of categories of improvement and decline language	03.07.17	
1Q18 annual review: Policies combined for Medicaid and commercial Expanded indication to SMA types 1-3 with SMN2 copies up to 4. References reviewed and updated	11.28.17	02.18
Added CHOP-INTEND score as an allowable tool to measure motor function for members < 2 years of age; allowed maintenance (in addition to improvement) from baseline CHOP-INTEND, HINE, or HFMSE score for continued approval; removed requirement for documentation of number of categories of improvement for continued approval; added HIM medical benefit line of business; references reviewed and updated.	05.08.18	08.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2019 annual review: no significant changes; references reviewed and updated.	11.20.18	02.19

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.