Clinical Policy: Nusinersen (Spinraza)

Reference Number: CP.PHAR.327
Effective Date: 03.01.17
Last Review Date: 02.22
Line of Business: Commercial, HIM, Medicaid

Coding Implications
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.

All requests reviewed under this policy **require medical director review**

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;
2. 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));
3. Prescribed by or in consultation with a neurologist;
4. Documentation of genetic testing quantifying number of copies of SMN2 gene and one of the following (a or b):
   a. One, two, or three copies of SMN2 gene;
   b. Four copies of SMN2 gene, and documentation indicates presence of SMA symptoms (e.g., weakness, tremors, loss of functionality);
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);

6. Member does not require tracheostomy or invasive or noninvasive ventilation for ≥ 16 hours/day continuously for > 21 days;
7. Failure* of a trial of Evrysdi®, unless contraindicated or clinically significant adverse effects are experienced;
   **Failure will be defined as decline in motor function test score(s) from baseline*
8. Spinraza is not prescribed concurrently with Evrysdi or Zolgensma®;
9. If the member is currently on Evrysdi, documentation of prescriber attestation of Evrysdi discontinuation upon initiation of Spinraza;
10. 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;
11. Total dose does not exceed 4 doses of 12 mg, prescribed for intrathecal use.

Approval duration: 12 months (up to 4 doses)

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Currently receiving medication for SMA with 1 to 4 copies of the SMN2 gene, or member has previously met initial approval criteria;
2. Member does not require tracheostomy or invasive or noninvasive ventilation for ≥ 16 hours/day continuously for > 21 days;
3. Member is responding positively to therapy, as evidenced by one of the following (a, b, or c):
   a. For age < 2 years, must meet one of the following (i or ii):
      i. For CHOP-INTEND, must demonstrate score improvement or maintenance of previous score improvement of ≥ 4 points from baseline;

ii. For HINE motor milestone score, must demonstrate score improvement or maintenance of previous improvement in one or more categories AND improvement in more motor milestone categories than worsening;

b. For age ≥ 2 years, one of the following (i, ii, or iii):
   i. If first renewal since turning 2 years old, must provide submission of baseline HFMSE score, RHS score, RULM or ULM score, or 6MWT distance AND meet one of the following (1 or 2):
      1) For CHOP-INTEND, must demonstrate score improvement or maintenance of previous score improvement of ≥ 4 points from baseline;
      2) For HINE motor milestone score, must demonstrate score improvement or maintenance of previous improvement in one or more categories AND improvement in more motor milestone categories than worsening;
   ii. If ≤ 2 years at therapy initiation and request is for subsequent renewal since turning 2, must meet one of the following (1 or 2) (*see Appendix D)*:
      1) For HFMSE, RHS, ULM or RULM, must demonstrate score improvement or maintenance of previous score improvement from baseline score submitted at first renewal since turning 2 years old;
      2) For 6MWT distance, must demonstrate improvement or maintenance of baseline distance;
   iii. If > 2 years at therapy initiation, must meet one of the following (1, 2, 3, or 4) (*see Appendix D)*:
      1) For HFMSE or RHS, must demonstrate score improvement or maintenance of previous score improvement of ≥ 3 points from baseline;
      2) For ULM, must demonstrate score improvement or maintenance of previous improvements in ≥ 2 points from baseline;
      3) For RULM, must demonstrate score improvement or maintenance of previous improvements in ≥ 4 points from baseline;
      4) For 6MWT distance, must demonstrate improvement or maintenance of baseline distance;
   c. Member has not had a decline in motor function test score(s) from baseline AND medical justification demonstrates and supports that member is responding positively to therapy;

4. Spinraza is not prescribed concurrently with Evrysdi or Zolgensma;
5. 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, 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
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 for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Evrysdi® (risdiplam)	Weight-based dose PO QD: • 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 • 2 years of age and older, weigh 20 kg or more: 5 mg	5 mg/day

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. HFMSE has demonstrated reliability and validity in patients with SMA. An increase of greater than 2 points in total score is unlikely in untreated SMA.
- 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.

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.; June 2020. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed September 21, 2021.
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.
10. Dunaway Young S, Montes J, Kramer SS, et al. Six-minute walk test is reliable and valid in spinal muscular atrophy. *Muscle and Nerve.* 2016. 54: 836-842.
11. Ramsey D, Scoto M, Mayhew A, et al. Revised Hammersmith Scale for Spinal Muscular Atrophy: A SMA Specific Clinical Outcome Assessment Tool. *PLoS ONE*. 2017; 12(2): e0172346. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0172346
12. Michelson D, Ciafaloni E, Ashwal S, et al. Evidence in focus: Nusinersen use in spinal muscular atrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018; 91:923-933. doi:10.1212/WNL.0000000000006502.

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	P&T Approval Date
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	05.08.18	08.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
approval; added HIM medical benefit line of business; references reviewed and updated.		
1Q 2019 annual review: no significant changes; references reviewed and updated.	11.20.18	02.19
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.	07.23.19	08.19
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.	10.09.19	11.19
1Q 2020 annual review: no significant changes; added HIM line of business; references reviewed and updated.	12.04.19	02.20
Amended re-authorization criteria to include validated functional tests: RHS, ULM, RULM, 6MWT; added objective paramenters defining improvement in continuation criteria.	02.13.20	02.20 (ad hoc)
Clarified that SMN2 genetic test results should be dated within the past year with repeat test for confirmation.	03.20.20	
Removed criteria requiring type of SMA, genetic tests within the last year, and repeat testing; amended language to require quantification of SMN2 copy number; amended re-authorization criteria to allow for medical justification.	07.07.20	08.20
Updated criteria language to restrict concomitant use with Evrysdi; references reviewed and updated.	08.25.20	11.20
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; updated HCPCS code; references reviewed and updated.	10.12.20	02.21
Added disclaimer under Policy/Criteria "All requests reviewed under this policy **require medical director review."**	05.04.21	
Added requirement for a trial of Evrysdi.	07.20.21	08.21
1Q 2022 annual review: revised continued therapy language to allow members to receive the medication for the appropriate indication if they had initiated the treatment outside of Centene benefit; references reviewed and updated.	09.21.21	02.22
Template changes applied to other diagnoses/indications.	09.21.22	

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.

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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.