RXADVANCE
2 Park Central Drive
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Clinical Policy Title:	nusinersen
Policy Number:	RxA.494
Drug(s) Applied:	Spinraza®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Nusinersen (Spinraza®) is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide. It is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
nusinersen (Spinraza®)	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

Dosage Forms

- Solution for intrathecal injection: 12 mg/5 mL (2.4 mg/mL) single dose vial

Clinical Policy

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

I. Initial Approval Criteria

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

1. Diagnosis of SMA Types I, II, or III;
2. Prescribed by or in consultation with a neurologist;
3. Genetic testing confirming 1, 2, 3, or 4 copies of SMN2 gene;
4. 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));

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. Member does not require tracheostomy or invasive or noninvasive ventilation for ≥ 16 hours/day continuously for > 21 days;
7. Spinraza® is not prescribed concurrently with Zolgensma®;
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. Total dose does not exceed 4 doses of 12 mg, prescribed for intrathecal use.

Approval Duration
Commercial: 12 months (up to 4 doses)
Medicaid: 12 months (up to 4 doses)
HIM: 12 months (up to 4 doses)

II. Continued Therapy Approval

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

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member does not require tracheostomy or invasive or non-invasive ventilation for ⩾ 16 hours/day continuously for > 21 days;
3. 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)*;
4. Spinraza® is not prescribed concurrently with 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
Commercial: 12 months
Medicaid: 12 months
HIM: 12 months

III. Appendices

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
- Contraindication(s):
  - None reported

- Boxed Warning(s):
  - 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 o 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.

References

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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.
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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.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Drug(s) Applied was updated. 3. Line of business policy applies was updated to All lines of business. 4. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 5. Initial Approval criteria: Commercial, Medicaid and HIM approval duration were updated to 6 months. 6. Continued Approval criteria:	09/04/2020	12/07/2020

Commercial, Medicaid and HIM approval duration were updated to 12 months. 7. References were reviewed and updated. 8. Dosage Form updated: Solution for intrathecal injection: 12 mg/5 mL (2.4 mg/mL) single dose vial		