Medical Coverage Policy | Spinraza (nusinersen)

EFFECTIVE DATE: 07|16|2019
POLICY LAST UPDATED: 07|16|2019

OVERVIEW

Spinal muscular atrophy (SMA) is an inherited disorder caused by homozygous deletions or variants in the *SMN1* gene. As a consequence of absent or low levels of SMN1 protein, the motor neurons in spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk. Nusinersen is a synthetic antisense oligonucleotide designed to bind to a specific sequence in exon 7 of the SMN2 transcript causing the inclusion of exon 7 in the SMN2 transcript, leading to production of full length functional SMN2 protein, which is very similar to SMN1.

This policy is applicable to BlueCHiP for Medicare products only. For Commercial Products, see related policy section

MEDICAL CRITERIA

BlueCHiP for Medicare
Initial Evaluation
Spinraza (nusinersen) will be approved when ONE of the following are met:

1. There is documentation that the patient is currently being treated with the requested agent
   OR
2. ALL of the following: a. The patient has a diagnosis of Spinal Muscular Atrophy (SMA) type I (Werdnig-Hoffmann disease), type II, or type III and the following:
   a. The prescriber has provided documentation of genetic testing confirming the patient has ONE of the following:
      i. Homozygous deletion of SMN1 gene
      OR
      ii. Homozygous absence of SMN1 gene due to gene conversion (i.e. SMN1 gene conversion to SMN2 gene)
      OR
      iii. Compound heterozygote mutation of SMN1 gene
   AND
   b. The prescriber has provided documentation confirming the patient has two or more copies of SMN2 gene as determined by genetic testing
   AND
   c. If the patient has ONE of the following:
      i. Type I or II and the prescriber has provided documentation indicating the patient had onset of SMA symptoms at or before 21 months of age
      OR
      ii. Type III and the prescriber has provided documentation indicating the patient's onset of SMA symptoms occurred after 18 months of age

   AND
3. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
4. The prescriber is a specialist (e.g. neurologist, geneticist) or the prescriber has consulted with a specialist for the diagnosis and management of SMA
   AND
5. The requested dose is within FDA approved labeling

Length of Approval:
Up to 6 months. NOTE: For patients initiating therapy, approval will include 4 initial loading doses and 1 maintenance dose for the remainder of the 6 months.

Renewal Evaluation

1. The patient has been previously approved for the requested agent through the Prime Therapeutics or BCBSRI PA or Medical Review process
   AND
2. The patient has received clinical benefit from the requested agent (e.g. stabilization or slowing of disease progression, decrease in symptom severity and/or frequency)
   AND
3. ONE of the following
   a. The requested dose is within FDA labeling
      OR
   b. The requested dose for the requested diagnosis is supported by compendia (NCCN Compendium™[level of evidence 1, 2A], AHFS, DrugDex [FDA approved Class I or Class IIa])
      OR
   c. The requested dose is outside the dose supported by FDA labeling or compendia AND the patient is currently taking and is stable on this dose
      OR
   d. The request is for a change in dose that is outside that supported by FDA labeling or compendia AND the prescriber has submitted documentation (the dose is supported by clinical research in 2 or more peer reviewed medical journals) in support of therapy with a higher dose for the requested diagnosis

Length of Approval: Up to 12 months

PRIOR AUTHORIZATION

Prior authorization is required for BlueCHiP for Medicare.

POLICY STATEMENT

BlueCHiP for Medicare

Spinrava (Nusinersen) may be considered medically necessary when the medical criteria are met.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable physician administered drug benefits/coverage.

BACKGROUND

Spinal Muscular Atrophy

Spinal Muscular Atrophy (SMA) is an autosomal recessive genetic disease characterized by muscle weakness and atrophy due to degeneration of spinal motor neurons. It is the second most common fatal autosomal recessive disorder after cystic fibrosis. It affects approximately 1 in 6000 to 10,000 live births. SMA occurs as a result of deletion or mutation of the survival motor neuron 1 (SMN1) gene which codes for the SMN protein. The consequence of absent or non-functional SMN1 protein is degeneration of the motor neurons resulting in atrophy of the voluntary muscles of the limbs and trunk. A second gene, SMN2, is also capable of coding for the SMN protein. However, SMN2 frequently leads to production of a truncated SMN protein that is dysfunctional and easily degraded. Nusinersen, an antisense oligonucleotide, binds to SMN2 thereby promoting production of higher levels of functional SMN protein.

Current literature indicates the number of SMN2 gene copies generally correlates with SMA phenotypes such that the higher the number of SMN2 gene copies, the milder the disease.

Patients suspected of having SMA should have the diagnosis confirmed by genetic testing. This is often done by a neurologist or geneticist. A positive diagnosis can be made if the patient is found to have homozygous deletion or conversion of SMN1 gene to SMN2 gene. 95% of SMA patients are diagnosed in this manner. The remainder (3 – 5%) of SMA patients can have the diagnosis confirmed if found to have compound heterozygous mutation of SMN1 gene.

SMA can be classified into different types based on varying severity and age of onset. Type 0 is very rare while type 1 is the most common accounting for 60% to 70% SMA. Type II is less severe than type 0 and type I and accounts for 20% to 30% of SMA. Type III and IV are milder forms of SMA that together account for 10% to 20% of SMA.

Clinical Classification of Spinal Muscular Atrophy

SMA Type[2,6]	Age of Onset	Usual # of SMN2 gene copies[6]	Characteristics	Highest Function	Natural Age of Death
Type 0 (severe)	Prenatal	1	Loss of fetal movement during later stages of pregnancy, little motor function at birth, inability to breath or swallow independently	None achieved	< 6 months
Type 1* (severe)	0 – 6 months	2	Weakness and hypotonia, paradoxical breathing, difficulty swallowing, feeding, and handling secretions	Never sits	< 2 years
Type 2 (intermediate)	7 – 18 months	2 – 4 (80% have 3 copies)	Bulbar weakness, difficulty swallowing, diaphragmatic breathing, difficulty clearing tracheal secretions, fine tremors	Never stands	> 2 years
Type 3 (mild)	> 18 months	80% have 4 copies	Muscle and joint aches, difficulty swallowing and coughing, hypoventilation, loss of ambulation, scoliosis	Stands and walks	Adult
Type 4 (adult)	Second or third decade	≥ 4	Mild motor impairment without respiratory or gastrointestinal problems	Walks during adult years	Adult

* Also referred to as Werdnig-Hoffmann disease

Considering vast clinical presentation of SMA, patient care should be tailored to the specific patient needs and include respiratory support, physical therapy, and nutritional support.

Nusinersen Safety

The most common adverse reactions in patients treated with nusinersen include lower respiratory infection, upper respiratory infection, and constipation. Nusinersen is associated with increased risk for bleeding complications and renal toxicity. It is therefore, recommended to obtain platelet count, coagulation laboratory levels, and quantitative spot urine protein level prior to each dose. Nusinersen does not have an FDA labeled contraindication.

Nusinersen Efficacy

The efficacy of nusinersen, upon which its FDA approval was granted, is based on results of a double-blind, sham-procedure controlled trial (ENDEAR) in symptomatic infantile-onset SMA (type I) patients. Its efficacy was further supported by open-label trials conducted in pre-symptomatic and symptomatic SMA patients. Efficacy of nusinersen in patients with later-onset SMA was evaluated in a separate phase III clinical trial (CHERISH).

ENDEAR

This was a phase III, double-blind, randomized, sham-procedure controlled study to assess efficacy, safety, and tolerability of nusinersen in patients with symptomatic infantile-onset SMA. Patients (n=121) were randomized 2:1 to receive either nusinersen or sham-procedure control. Key inclusion criteria included the following: onset of SMA symptoms before 6 months of age, age ≤ 7 months at the time of the first dose and two copies of the SMN2 gene. The primary outcome was proportion of responders (i.e. improvement in motor milestones according to section 2 of the HINE) and was assessed at study day 183 and onwards. Treatment responders were defined as those with at least a 2 point increase in ability to kick, or at least a 1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking.
An interim analysis of the results was evaluated among 82 patients who were eligible. A statistically significant percent of patients in the nusinersen arm achieved motor milestone response compared to those in the sham-procedure arm. The trial also assessed treatment effects using the CHOP-INTEND, a tool that evaluates motor skills in patients with infantile-onset SMA.

Motor Milestone Response (HINE section 2) and CHOP-INTEND results

Endpoint	SPINRAZA-treated patients (n=52)[1]	Sham-control patients (n=30)[1]
Motor Milestone (HINE Section 2)		
Achievement of a motor milestone response	21 (40%) p<0.0001	0 (0%)
CHOP-INTEND Improvement from Baseline[2]		
At least 4-points	33 (63%)	1 (3%)
CHOP-INTEND Worsening from Baseline[2]		
At least 4-points	2 (4%)	12 (40%)

[1]Analyses included all subjects who were alive with the opportunity for at least a 6-month (Day 183) assessment and all subjects who died or withdrew from the study at the time of the interim analysis
[2]Not statistically controlled for multiple comparisons at interim analysis

CHERISH
This was a phase III, double-blind, randomized, sham-procedure controlled study of nusinersen in patients with later-onset SMA consistent with type II SMA. Subjects were randomized to receive nusinersen (n=84) or a sham-procedure control (n=42). The trial enrolled patients with onset of SMA symptoms at greater than 6 months of age and all patients had symptom onset by 21 months. The patients were required to be able to sit independently and to have never had the ability to walk independently. The primary end point was change in baseline HFMSE score at 15 months. HFMSE is a tool used to assess motor function in children with SMA. Patients enrolled in the trial were required to have a baseline HFMSE score of ≥ 10 and ≤ 54. A change of ≥3 points in the HFMSE is estimated to represent a clinically meaningful improvement.

An interim analysis of the results at study month 15 was conducted among 54 patients who were eligible for the analysis. The results showed a statistically significant change from baseline in the HFMSE score in the nusinersen group (4.0 (95% CI: 2.9-5.1)) compared to the sham-procedure control group (-1.9 (95% CI: -3.8-0.0)) (p=0.0000002). In the end of study analysis, the treatment difference in change from baseline to Month 15 in mean HFMSE score also was highly clinically and statistically significant (4.9 points: nusinersen, 3.9-point improvement; sham procedure control, 1.0-point decline; nominal. P=.000000). There were no treatment discontinuations due to adverse events.

Based on the results of the interim analysis, the CHERISH trial was stopped. All participants could then elect to enroll in SHINE, an open-label trial evaluating the long term safety and tolerability of nusinersen. SHINE is ongoing at the time of this writing (February 2017). A second, ongoing trial (NURTURE), is evaluating efficacy and safety of nusinersen in pre-symptomatic infants genetically diagnosed with SMA.

CODING

Blue CHiP for Medicare
The following HCPCS code is covered when the medical criteria have been met:
J2326 Injection, nusinersen, 0.1 mg

RELATED POLICIES
Prior Authorization of Drugs

PUBLISHED
Provider Update September 2019
Provider Update June 2018
Provider Update May 2017

REFERENCES:

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4. Prior T and Finanger E. Spinal Muscular Atrophy. National Center for Biotechnology Information (NCBI). Available at . Accessed February 2017.
5. De Sanctis R, Coratti G, Pasternak A, et al. Developmental milestones in type I spinal muscular atrophy. *Neuromuscular Disorders.* 2016;26(11):754-759. doi:10.1016/j.nmd.2016.10.002.
6. FDA Summary review of nusinersen. Available at. Accessed February 2017.
7. A Study to Assess the Efficacy and Safety of IONIS-SMNRx in Patients with Later-onset Spinal Muscular Atrophy. Available at Accessed February 2017.
8. Muralidharan K, Wilson RB, Ogino S, Nagan N, Curtis C, Schrijver I. Population Carrier Screening for Spinal Muscular Atrophy: A Position Statement of the Association for Molecular Pathology. *The Journal of Molecular Diagnostics : JMD.* 2011;13(1):3-6. doi:10.1016/j.jmoldx.2010.11.012.

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