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Subject: Nusinersen (Spinraza™)

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DESCRIPTION:

Spinal muscular atrophy (SMA) is a group of genetic disorders characterized by a loss of motor neurons. While there are numerous gene mutations that can cause the different forms of SMA, 95% of cases result from a homozygous deletion or mutation in the 5q13 survival of motor neuron (SMN1) gene. This deficiency results in degeneration of motor neurons causing muscle atrophy, particularly in the limbs and the muscles that control the mouth, throat and respiration. A second gene, SMN2, is nearly identical to SMN1 but does not produce much functional (i.e., full length, stable) SMN protein. While there is generally one SMN1 per chromosome, there is a variable number of SMN2 gene copies.

The severity of SMA (an autosomal recessive disorder) is highly variable and correlates mainly with the number of SMN2 gene copies. The clinical features can be classified based on the age of onset and maximum motor function (table 1).

Table 1. SMA Classification

Type	Age of onset	Highest Function	Natural Age of Death	Copies of SMN2
0	Prenatal	Respiratory failure	< 1 month	1
I (Werdnig-Hoffman disease)	0-6 months	Never sit	< 2 years	2
II (Dubowitz disease)	< 18 months	Never stand	> 2 years	3, 4
III (Kugelberg-Welander disease)	18 months-21 years	Stand or ambulatory	Adult	3, 4
IV (adult onset)	> 21 years	Ambulatory	Adult	4-8

The incidence of SMA is approximately 1 in 11,000 live births and it is reported to be the leading genetic cause of infant death. Carrier frequencies are estimated at 1 in 40 to 1 in 60. SMA can be diagnosed by DNA analysis detection of SMN1 deletion in both SMN1 alleles. This is approximately 95% sensitive (100% specific) for patients with clinical features suspicious for SMA.

There is no known cure for SMA. Treatment is designed to address the primary and secondary effects of muscle weakness and includes management of pulmonary complications, nutritional and gastrointestinal support, orthopedic care, rehabilitative interventions, and end-of-life care.

Nusinersen (Spinraza), an antisense oligonucleotide, was approved by the U.S. Food and Drug Administration (FDA) in December 2016 for the treatment of the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. The approval was based on positive interim results of a phase III, double-blind, controlled clinical trial (ENDEAR).

The safety and efficacy of nusinersen were evaluated in in infants, aged 7 months or younger at study entry, who were diagnosed with symptomatic infantile-onset SMA (Type I). Patients were required to have a confirmatory diagnosis of SMA consistent with type I severity as determined by identification of two copies of SMN2, age of onset (symptom onset before 6 months of age), and symptom severity. A total of 82 infants out of 121 enrolled were included in the interim analysis. Study participants were enrolled 2:1 and all infants included in the interim analysis had died, withdrawn or completed at least 183 days (6 months) of treatment. Baseline disease characteristics were similar between study arms with the exception of the nusinersen-treatment group having a higher percentage of paradoxical breathing, pneumonia, respiratory symptoms, swallowing/feeding difficulty and need for respiratory support. Despite the treatment group having more severe symptoms at baseline, the trial found 40% of those treated, compared with 0% of those in the control arm, demonstrated improvement in motor milestones such as head control, sitting, crawling and standing ($p<0.0001$). Furthermore, as assessed by the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), 63% (n=33) of infants treated with nusinersen improved by at least 4-points, whereas only 3% (n=1) achieved this improvement in the control arm. Similarly, 40% (n=12) of the control arm worsened by at least 4-points on the CHOP-INTEND test whereas only 4% (n=2) of the treatment arms experienced this decline in motor function. The adverse events that occurred in the treatment arm more often than the control arm were respiratory infections and constipation. Atelectasis, a serious adverse reaction, was more frequent in the treatment arm (14%) compared to the control arm (5%).

In April 2017, the results of CHERISH, a phase III, double-blind, controlled clinical trials of nusinersen in later-onset SMA, were presented at the American Academy of Neurology annual meeting. Patients with SMA were included if they were 2-12 years of age and had an onset of SMA symptoms after 6 months of age. Participants were randomized 2:1 (stratified based on screening age <6 versus ≥6 years) to receive 4 doses of intrathecal nusinersen (12mg non-scaled) or sham procedure over 15 months. The primary endpoint was change in the Hammersmith Functional Motor Scale–Expanded (HFMSE) score at month 15. The HFMSE evaluates performance on 20 items and assigns a score of 0 (unable to complete), 1 (performed with compensation), or 2 (performed unaided) for a maximum of 40 points. Secondary endpoints included proportion of children with ≥3-point increase in HFMSE score, proportion with achievement of new WHO motor milestones, and change in revised Upper Limb Module (RULM) test at month 15.

CHERISH enrolled 126 children and 100% had symptom onset by 21 months of age. The change from baseline in HFMSE score was significantly different in the nusinersen arm versus the control arm (4.9 point difference; $p<0.000$), with a mean improvement of 3.9 points in the nusinersen arm and a mean 1.0-point decline in the control arm. There were no treatment-related discontinuations related to adverse events and no new safety concerns emerged.

POSITION STATEMENT:

Initiation of nusinersen (Spinraza) **meets the definition of medical necessity** when all of the following criteria are met:

1. Indication for use is spinal muscular atrophy (SMA)
2. Member's diagnosis has been confirmed by either of the following:
    a. Homozygous deletion of SMN1 gene exon 7 (with or without deletion of exon 8) – laboratory documentation must be provided
    b. Single copy of SMN1 with sequencing of the coding region to confirm a mutation rendering a homozygous dysfunction of the gene – laboratory documentation must be provided
3. Member has an onset of clinical signs and symptoms of SMA prior to 21 months of age – documentation from the medical record must be provided
4. Treatment is prescribed by or in consultation with a board certified (or board eligible) neurologist
5. **ONE** of the following:
    a. Member has not previously received gene therapy (including Zolgensma) for SMA
    b. Member previously received gene therapy **AND** was unable to maintain beneficial response in SMA-associated symptoms – documentation from the medical record must be provided
6. Member is not concurrently enrolled in a clinical trial to receive an experimental therapy for SMA
7. Dose does not exceed **BOTH** of the following:
    a. Loading: 12 mg (1 vial) for 4 doses
        i. First three loading doses are administered every 14 days (on day 1, day 15, day 29)
        ii. Fourth loading dose is administered 30 days after the third dose (on day 59)
    b. Maintenance: 12 mg (1 vial) every 4 months (3 doses/year)
        i. First maintenance dose is administered at least 4 months after the fourth loading dose

Approval duration: 1 year (maximum 6 vials)

Continuation of nusinersen (Spinraza) **meets the definition of medical necessity** when all of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue in the past two years for treatment of spinal muscular atrophy (SMA), **OR** the member has previously met all indication-specific initiation criteria
2. Member's diagnosis has been confirmed by either of the following:
    a. Homozygous deletion of SMN1 gene exon 7 (with or without deletion of exon 8) – laboratory documentation must be provided
    b. Single copy of SMN1 with sequencing of the coding region to confirm a mutation rendering a homozygous dysfunction of the gene – laboratory documentation must be provided

3. Member has demonstrated a beneficial response in SMA-associated symptoms – documentation from medical record must be provided
4. Treatment is prescribed by or in consultation with a board certified (or board eligible) neurologist
5. Dose does not exceed 12 mg (1 vial) every 4 months (3 doses/year)

Approval duration: 1 year (maximum 3 vials)

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- The recommended dosage is 12 mg (5 mL) per administration
- Initiate treatment with 4 loading doses; the first three loading doses should be administered at 14-day intervals; the 4th loading dose should be administered 30 days after the 3rd dose; a maintenance dose should be administered once every 4 months thereafter

Dose Adjustments

- None

Drug Availability

- Injection: 12 mg/5 mL (2.4 mg/mL) in a single-dose vial

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- Thrombocytopenia and Coagulation Abnormalities: Increased risk for bleeding complications; testing required at baseline and before each dose
- Renal Toxicity: Quantitative spot urine protein testing required at baseline and prior to each dose

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J2326	Injection, nusinersen, 0.1 mg

CPT Coding

96450	Chemotherapy administration, into central nervous system (CNS) (eg, intrathecal), requiring spinal puncture
62270	Spinal puncture, lumbar, diagnostic
62272	Spinal puncture, therapeutic, for drainage of cerebrospinal fluid (by needle or catheter)

ICD-10 Diagnosis Codes That Support Medical Necessity

G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]
G12.1	Other inherited spinal muscular atrophy
G12.8	Other spinal muscular atrophies and related syndromes
G12.9	Spinal muscular atrophy, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 08/14/19.

GUIDELINE UPDATE INFORMATION:

03/15/17	New Medical Coverage Guideline.
07/01/17	Addition of HCPCS code C9489.
08/15/17	Revision to guideline consisting of description and position statement.
12/15/17	Revision to guideline consisting of updating position statement
01/15/18	Review and revision to guideline; updating position statement, coding, references.
08/08/18	Revision to guideline consisting of updating position statement
01/15/19	Revision to guideline consisting of updating position statement
09/15/19	Revision to guideline consisting of updating position statement