Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

Title: Spinraza™ (nusinersen)

- **Prime will review Prior Authorization requests**

Prior Authorization Form:
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-Spinraza.pdf

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

Professional
Original Effective Date: May 31, 2017
Revision Date(s): May 31, 2017
Current Effective Date: May 31, 2017

Institutional
Original Effective Date: May 31, 2017
Revision Date(s): May 31, 2017
Current Effective Date: May 31, 2017

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

The intent of the Spinraza (nusinersen) Medical Drug Criteria is to appropriately select patients for treatment with nusinersen based on FDA approved labeling and/or clinical practice guidelines. This program will require the patient has Spinal Muscular Atrophy (SMA) type I or type II as confirmed by genetic testing. The program will also require the patient had onset of SMA symptoms at or before 18 months of age. Therapy must have been prescribed by an SMA specialist or in consultation with one. The program will

require the prescribed dose is within FDA labeling. Initial approval will be for 6 months. Subsequent approvals for continuation of therapy will be for 12 months when the patient demonstrates clinical improvement or disease stabilization from treatment with nusinersen.

Target Agent

- **Spinraza™** (nusinersen)

FDA Approved Indications and Dosage[1]

Agent(s)	Indication	Dosing*
Spinraza™ (nusinersen)	Spinal muscular atrophy in pediatric and adult patients	**Initial (loading) doses:** 12 mg (5mL) intrathecally every 14 days for 3 doses followed by a 4th loading dose of 12 mg (5mL) intrathecally 30 days after the 3rd loading dose. **Maintenance dose:** 12 mg (5mL) intrathecally once every 4 months

*If a loading dose is delayed or missed, administer nusinersen as soon as possible, with at least 14-days between doses and continue dosing as prescribed. If a maintenance dose is delayed or missed, administer nusinersen as soon as possible and continue dosing every 4 months.

POLICY

Initial Evaluation

Spinraza (nusinersen) will be approved when ALL of the following are met:

1. The patient has a diagnosis of Spinal Muscular Atrophy (SMA) type I (Werdnig-Hoffmann disease) or type II
   AND
2. The prescriber has provided documentation of genetic testing confirming the patient has ONE of the following:
   a. Homozygous deletion of SMN1 gene
      OR
   b. Homozygous absence of SMN1 gene due to gene conversion (i.e. SMN1 gene conversion to SMN2 gene)
      OR
   c. Compound heterozygote mutation of SMN1 gene
   AND
3. The prescriber has provided documentation confirming the patient has two or more copies of SMN2 gene as determined by genetic testing
   AND

4. The prescriber has provided documentation indicating the patient had onset of SMA symptoms at or before 18 months of age
   AND
5. The patient does not have any FDA labeled contraindications to therapy with the requested agent
   AND
6. The requested agent is prescribed by a prescriber (e.g. neurologist, geneticist) that specializes in the diagnosis and management of SMA or in consultation with a prescriber that specializes in the diagnosis and management of SMA
   AND
7. 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

Spinraza (nusinersen) will be approved for continued use when ALL of the following are met:

1. The patient was previously approved for the requested agent through the Prime Therapeutics Medical Drug Review process
   AND
2. The prescriber has provided documentation indicating the patient has had disease stabilization or clinical improvement in the symptoms* of SMA (*e.g. motor function, limb and trunk weakness, hypotonia and impaired head control, difficulty breathing, swallowing, feeding, and handling secretions etc)
   AND
3. The patient does not have any FDA labeled contraindications to therapy with the requested agent
   AND
4. The requested agent is prescribed by a prescriber (e.g. neurologist, geneticist) that specializes in the diagnosis and management of SMA or in consultation with a prescriber that specializes in the diagnosis and management of SMA
   AND
5. The requested dose is within FDA approved labeling

Length of Approval: Up to 12 months

Agent	Contraindications
Spinraza™ (nusinersen)	None

Spinraza Dosing

Agent	Initial (loading) Doses	Maintenance dose
Spinraza (nusinersen)	12 mg (5mL) intrathecally every 14 days for 3 doses followed by a 4th loading dose of 12 mg (5mL) intrathecally 30 days after the 3rd loading dose.	12 mg (5mL) intrathecally once every 4 months following the loading doses

Brand (generic)	Quantity Limit
Spinraza™ (nusinersen)	
12 mg/5 mL single use vial	3 vials

RATIONALE

Spinal Muscular Atrophy[1-6,8]

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[2,6]	Usual # of SMN2 gene copies[6]	Characteristics[2]	Highest Function[2,6]	Natural Age of Death[2]
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[3]

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[1]

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[1]

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[1]

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[7,9]

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. 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).

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.

REVISIONS

05-31-2017	Policy published 05-01-2017. Policy effective 05-31-2017.

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