EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Spinraza™ (nusinersen injection for intrathecal use – Biogen)

TAC APPROVAL DATE: 01/25/2017

LAY CRITERIA EFFECTIVE DATE: 03/15/2017

OVERVIEW

Spinraza, a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[1] Reduced levels of survival motor neuron (SMN) protein, due to homozygous deletions or mutations to the survival motor neuron-1 (SMN1) gene, are believed to be the cause of spinal muscular atrophy. Spinraza increases full-length SMN protein by targeting the process through which it is produced by the SMN2 gene. Spinraza is given intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures. The recommended dosage is 12 mg (5 mL) per administration. Initiate Spinraza treatment with four loading doses. The first three loading doses should be administered at 14-day intervals. The fourth loading dose should be given 30 days after the third dose. A maintenance dose should be given once every 4 months thereafter. The most common adverse events (AEs) with Spinraza were lower respiratory tract infection (43%), upper respiratory tract infection (39%), and constipation (30%). Spinraza has Warnings/Precautions regarding thrombocytopenia and coagulation abnormalities, as well as renal toxicity. Due to the increased risk of bleeding complications and renal toxicity, testing is required at baseline and prior to each dose.

Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder that is clinically characterized by progressive muscle weakness and atrophy.[2-8] It is more frequently diagnosed in infants and children and it is the most common genetic cause of death in infants.[6] Proximal muscles (e.g., torso, legs, neck) are more impacted compared with distal muscles (e.g., hands, arms, feet). Patients with spinal muscular atrophy may never be able to, or progressively lose the ability to walk, stand, sit and/or ambulate. More severe disease manifests with poor head control (hypotonia), reduced reflexes, tongue movements and difficulties in swallowing and feeding. Respiratory illnesses and bone and/or spinal deformities may occur. However, cognitive development is not impacted. The incidence of spinal muscular atrophy is estimated to be 1 per 6,000 to 10,000 live births and is believed to impact as many as 10,000 to 25,000 children and adults in the US.[3-4,7-8] Although it can vary among ethnic groups, the estimated carrier frequency ranges from 1 in 40 to 1 in 60 individuals; there are approximately 6 million carriers in the US.[3-4,7] The disorder is caused by an abnormal or missing gene known as SMN1, which is found on chromosome 5q (in band 13) and produces a protein essential to motor neurons.[5,8] Devoid of this protein, lower motor neurons in the spinal cord do not function properly, can degenerate and die.

The genetics of spinal muscular atrophy are complex.[3-4,5,8] Most people have two nearly identical SMN genes, SMN1 and SMN2. There are also copies, sometimes multiple, of these two genes.[3-4] SMN1 is responsible for producing most of the effective SMN protein, although some SMN protein is made by the SMN2 gene. Therefore, patients with a deletion of the SMN1 gene may have the potential for making some functional protein through the SMN2 gene, although in most cases the resulting SMN2 protein is truncated and is not as effective. The disease has a variable phenotypic expression due to the amount of the SMN protein produced, as well as due to backup copies of the gene.[3-4] Data have shown that patients

with a higher number of SMN2 copies generally have a more mild phenotypic disease expression. Diagnostic testing for spinal muscular atrophy can be performed at many laboratories.[4]

Spinal muscular atrophy is generally divided into five different types, which differ in various aspects such as the age of onset, clinical severity, and life expectancy.[4-6] Type 0 is the most severe form and progresses during pregnancy. Fetal movement may be reduced *in utero* and development is delayed. Respiratory distress occurs at birth, which may require a respirator, and death frequently occurs within weeks. Type I generally occurs or manifests around or before the patient is 6 months of age. The symptoms are hallmarked by patients not being able to control head movement. Developmentally, patients are unable to sit without assistance. The life expectancy is usually less than 3 years of age. Type II disease has an onset between 6 to 18 months. Patients are generally able to sit independently; however, the ability to walk is usually not achieved without assistance. The lifespan is generally between 10 to 40 years. Type III typically manifests after the patient is 18 months of age or older. Some patients lose the ability to walk in adulthood whereas others may be able to walk without assistance throughout their normal lifespan. Type IV is the mildest form of the disease. Symptoms of muscle weakness occur in adulthood (middle to late age) but patients usually retain the ability to walk. Lifespan is generally not reduced due to the disease. The incidence of the severe disease types (type 0 and type I) is higher but due to the shortened lifespan, the prevalence is less; type IV disease is not common. A different manner of categorization classifies the main three most common types as follows: type I patients are "non-sitters", type II patients are "sitters", and type III patients are "walkers".

CLINICAL EFFICACY

Spinraza was investigated in a pivotal trial called ENDEAR, which was a Phase III, multicenter, multinational, randomized, double-blind, sham-procedure controlled, unpublished study involving 121 symptomatic infants diagnosed with spinal muscular atrophy (type I).[1-2] Patients were randomized 2:1 to receive either Spinraza (n = 80) or sham injection (n = 41).[1-2] Eligible patients were ≤ 7 months of age at the time of the first dose and diagnosed with spinal muscular atrophy with a symptom onset prior to 6 months of age.[1] A planned interim efficacy analysis was performed based on patients who died, withdrew, or completed at least 183 days of treatment. The mean age at first treatment was a median of 181 days (range, 30 to 262 days) and the median disease duration was 14 weeks. The primary endpoint assessed at the time of the interim analysis was the proportion of responders, defined as patients with improvement in motor milestones according to Section 2 of the Hammersmith Infant Neurologic Exam (HINE). This endpoint assesses seven different areas of motor milestone development with a maximum score of 26. A treatment responder was defined as any patient with at least a 2-point increase (or maximal score of 4) in the ability to kick (consistent with improvement by at least two milestones), or at least a 1-point increase in the motor milestones assessing head control, rolling, sitting, crawling, standing or walking (consistent with improvement by at least one milestone). To be categorized as a responder, the patient was required to display improvement in more categories of motor milestones than worsening. Although not statistically controlled for multiple comparisons at the interim analysis, the treatment effects on the Children's Hospital of Philadelphia Test of Neuromuscular disorders (CHOP-INTEND) were evaluated, which is also an assessment of motor skills in patients with infant-onset spinal muscular atrophy.[1] Due to the favorable results observed in the planned interim efficacy analysis the trial was stopped prior to the scheduled completion and all patients received open-label Spinraza therapy.[2] The median time of treatment was 261 days (range, 6 to 442 days).[1] Of the 82 patients deemed eligible for the interim analysis, a statistically significantly greater percentage of patients achieved a motor milestone response in the Spinraza group compared with the sham-procedure control group (40% [n = 21/52] vs. 0% [n = 0/30], respectively).[1] Also, more patients given Spinraza vs. sham-procedure control (63% vs. 3%,

respectively) achieved improvement from baseline of at least 4-points on the CHOP-INTEND, which assesses motor skills.

The prescribing information for Spinraza states that the results of the ENDEAR trial involving patients with infant-onset spinal muscular atrophy were supported by open-label uncontrolled trials performed in patients who were symptomatic with spinal muscular atrophy (age range at the time of the first dose, 30 days to 15 years) and in presymptomatic patients (age range at the time of the first dose, 8 days to 42 days).[1-2,9] The patients in these studies had, or were likely to develop, type I, II or III spinal muscular atrophy. Some patients reached milestones such as the ability to sit unassisted, stand, or walk when they would otherwise be unexpected to do so, maintained milestones at ages when they would be expected to be lost, and survived to ages unexpected considering the number of SMN2 gene copies of patients comprised in the studies. The overall findings of the ENDEAR trial and the open-label uncontrolled trials support the effectiveness of Spinraza across the range of patients with spinal muscular atrophy and appear to support early initiation of Spinraza treatment.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Spinraza. Because of the specialized skills required for evaluation and diagnosis of patients treated with Spinraza, as well as the monitoring required for AEs and long-term efficacy, initial approval requires Spinraza to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 1 year.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and/or laboratory data.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Spinraza is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Spinal Muscular Atrophy.** Approve for 1 year if the patient meets all of the following criteria (A, B and C):
   - **A)** The medication is prescribed by or in consultation with a physician who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND
   - **B)** The patient has type I, II or III spinal muscular atrophy; AND
   - **C)** The patient meets ONE of the following (i or ii):
     - **i.** The patient has had a genetic test which confirms the diagnosis of 5q spinal muscular atrophy by homozygous gene deletion, homozygous mutation, or compound heterozygous mutation **[documentation required]**; OR
     - **ii.** If a genetic test does not confirm the diagnosis of spinal muscular atrophy the patient must meet one of the following (a or b):
       - **a)** According to the prescribing physician, the patient has clinical signs and/or symptoms to indicate a diagnosis of spinal muscular atrophy (e.g., hypotonia, limb weakness, developmental motor delay [unable to sit or cannot walk independently at an expected

level based on the patient's age], paradoxical breathing, significant swallowing or feeding difficulties, and/or ventilation support is required) **[documentation required]**; OR

b) The patient has a family history of a first degree relative (e.g., parent or sibling) diagnosed with spinal muscular atrophy or is a genetic carrier **[documentation required]**.

Spinraza is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[1] Spinal muscular atrophy is a neurodegenerative disease.[3-8] For the majority of patients with spinal muscular atrophy (95%), the condition can be confirmed by genetic testing. Some of the signs and/or symptoms that patients experience due to the loss of muscle strength and movement include hypotonia, extreme limb weakness, developmental motor delay (cannot sit or walk independently when such milestones are expected), paradoxical breathing, significant swallowing or feeding difficulties, and/or requirement of ventilator support. Spinal muscular atrophy is an autosomal recessive genetic disorder inherited by the parents who are carriers. With Spinraza, data are available only in patients with type I, II or III disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Spinraza has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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