PRIOR AUTHORIZATION POLICY

POLICY: Spinal Muscular Atrophy – Zolgensma Prior Authorization Policy
- Zolgensma® (onasemnogene abeparvovec-xioi intravenous infusion – Novartis)

REVIEW DATE: 10/05/2022

OVERVIEW

Zolgensma, an adeno-associated virus vector-based gene therapy, is indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.[1]

Limitations of use are that the safety and effectiveness of repeat administration of Zolgensma have not been evaluated.[1] The use of Zolgensma in patients with advanced spinal muscular atrophy (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been assessed. Use of Zolgensma in premature neonates before reaching full-term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development. Zolgensma therapy should be delayed until full-term gestational age is achieved. The definition of full-term pregnancy commences at 39 weeks and 0 days gestation.[2]

Disease Overview

Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder caused by deletion or loss of function mutation in the SMN1 gene.[3-6] The reduced levels of survival motor neuron (SMN) protein causes degeneration of lower motor neurons.[6] Although the condition is a multisystem disorder, it is clinically characterized by progressive muscle weakness and atrophy. Patients have difficulties with ambulation, head control, feeding and respiration. Cognitive development is not impacted. In the US, spinal muscular atrophy affects approximately one in 11,000 infants and has an average carrier frequency of one in 54 individuals; as many as 10,000 to 20,000 children and adults in the US may be impacted.[6] Although the condition can be present in individuals of any age, it is more frequently diagnosed in infants and children, as it is more severe in this population.[3-6] The phenotypic expression of the disease is impacted by the presence of the survival motor neuron 2 (SMN2) gene copy number. SMN1 is responsible for producing most of the effective SMN protein, although some SMN protein can be made by the SMN2 gene. Therefore, patients with a deletion of the SMN1 gene may have the potential for making some SMN protein through the SMN2 gene copy, although in most cases the resulting protein made by this gene is truncated and is not as effective or functional. Data have shown that patients with a higher number of SMN2 gene copies generally have a more mild phenotypic disease expression. Gene deletion testing for spinal muscular atrophy can be performed at many diagnostic laboratories. Table 1 describes disease types. A different manner of categorization classifies the three most common types as follows: Type 1 patients are "non-sitters", Type 2 patients are "sitters", and Type 3 patients are "walkers".[4,6]

Table 1. Types of Spinal Muscular Atrophy.[3-6]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Gene Copy Number
0	Prenatal	Severe hypotonia and weakness; respiratory failure at birth. There is no achievement of motor milestones.	A few weeks to < 6 months	0 to 1
1	< 6 months	Poor muscle tone, lack of movement, and respiratory assistance needed at birth. Patients are never able to sit.	< 2 years	1 to 2

Table 1 (continued). Types of Spinal Muscular Atrophy.[3-6]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Gene Copy Number
2	Before 18 months	Patients are able to sit. However, patients are unable to walk or stand without assistance.	75% of patients are alive at 25 years of age	2 to 3
3	> 18 months	Walks independently but may lose this ability as the disease progresses.	Normal	3 to 4
4	Adulthood	Walk until adulthood.	Normal	≥ 4

SMA – Spinal muscular atrophy; SMN2 – Survival motor neuron 2.

Besides Zolgensma, other therapies are available. **Spinraza®** (nusinersen intrathecal injection), a SMN2-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[7] Spinraza is given by intrathecal injection. Although studies and experience continue, the primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children. Data are also available with Spinraza in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy. There is an accumulation of data with Spinraza in adults as well.

Evrysdi® (risdiplam oral solution), a SMN2 splicing modifier, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[8] The primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children and adults up to 25 years of age. Data are also available in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy.

Clinical Efficacy

The efficacy of Zolgensma was evaluated in patients less than 2 years of age with spinal muscular atrophy who had bi-allelic mutations in the SMN1 gene.[1,9-14] One trial was an open-label, single-arm study which is ongoing (STR1VE [n = 21])[11] and the other was an open-label, single-arm, ascending-dose clinical trial (START [n = 15] {12 patients received a therapeutic dose}).[1,9,10] Symptoms onset occurred before patients were 6 months of age. All patients had genetically confirmed bi-allelic SMN1 gene deletions and two SMN2 gene copies. In both trials, Zolgensma was given as a single-dose intravenous infusion. Efficacy was assessed on parameters such as survival and achievement of developmental motor milestones (e.g., sitting without support). The definition of survival was the time from birth to either death or permanent ventilation. Other efficacy parameters were evaluated (e.g., assessment of Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP-INTEND] scores, evaluation of ventilator use). The ongoing clinical trial involved 21 patients with infantile-onset spinal muscular atrophy. The mean CHOP-INTEND score was 31.0 (range, 18 to 47). The mean patient age at the time of treatment was 3.9 months (range 0.5 to 5.9 months). As of the March 2019 cutoff date, 19 patients were alive without permanent ventilation. Compared with natural history data, Zolgensma is effective as more patients attained the ability to sit without support.[1] The completed clinical trial involved 15 patients with infantile-onset spinal muscular atrophy.[1,9] Three patients were in a low-dose cohort and 12 patients were in a high-dose cohort.[1] At the time of treatment, the mean age of patients in the low-dose cohort was 6.3 months (range 5.9 to 7.2 months) and 3.4 months (range 0.9 to 7.9 months) in the high-dose group. The dose in the low-dose cohort was approximately one-third of the dosage received by patients in the high-dose cohort. At 24 months following Zolgensma infusion, one patient in the low-dose cohort met the endpoint of permanent ventilation; all 12 patients in the high-dose cohort were alive without permanent ventilation. In the high-dose cohort, 9 of 12 patients (75%) were able to stand and walk without assistance.[1,9] At longer-term follow-up from the START trial, all 10 patients followed in the high-dose group were alive without permanent ventilation at the dataset on June 11, 2020. In STR1VE, at the March 2019 data cutoff, 19 patients were alive without permanent ventilation.[1] Up until November 2019, data revealed that 13 of 22 patients achieved the coprimary endpoint of functional independent sitting for 30 seconds or longer at the 18 months of age study visit.[11] Other data are also available.[12-15]

Guidelines

The Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group is comprised of clinicians and geneticists with expertise in spinal muscular atrophy who developed a treatment algorithm in 2018 for infants who have positive results from a newborn screening test for spinal muscular atrophy.[16] Spinal muscular atrophy Types 1 and 2 comprise a large majority of cases and account for many patients who screen positively for spinal muscular atrophy with three or fewer SMN2 gene copies. Immediate treatment is recommended in patients with two or three SMN2 gene copies. Treatment recommendations for patients who screen positive for spinal muscular atrophy and have only one SMN2 gene copy is more complicated. It is likely that patients with only one SMN2 gene copy will likely be symptomatic at birth and the physician should determine if treatment is warranted.[16] In 2020, the Working Group updated recommendations that infants diagnosed with spinal muscular atrophy via newborn screening with four SMN2 gene copies should receive immediate treatment.[17] Also, patients with five (or more) SMN2 gene copies should be observed and screened for symptoms.

Dosing

The recommended dose of Zolgensma is 1.1×10^{14} vector genomes (vg) per kg of body weight.[1] Administer Zolgensma as an intravenous infusion over 60 minutes. Starting 1 day prior to Zolgensma infusion, give systemic corticosteroids equivalent to oral prednisolone 1 mg/kg of body weight for a total of 30 days. Examine liver function after this juncture and follow recommended guidelines.

Safety

Zolgensma has a Boxed Warning regarding acute serious liver injury and acute liver failure.[1] Elevated aminotransferases can occur with Zolgensma. Patients with preexisting liver impairment may be at higher risk. Prior to infusion, evaluate liver function in all patients by clinical examination and laboratory testing. One day before Zolgensma infusion, commence administration of systemic corticosteroids equivalent to oral prednisolone at 1 mg per kg of body weight per day for a total of 30 days. Transient decreases in platelet counts may occur. Therefore, measure platelet counts prior to the infusion, weekly for the first month, and then once every other week for the second and third month until platelet counts return to baseline. Also, temporary increases in cardiac troponin-I levels were noted with Zolgensma administration. Therefore, assess troponin-I prior to the infusion, as well as weekly for the first month and then monthly for the second and third month until troponin-I level returns to baseline. Perform baseline anti-AAV9 antibody testing prior to Zolgensma infusion. Patients in the Zolgensma trials were required to have baseline anti-AAV9 antibody titers of $\leq$ 1:50.

POLICY STATEMENT

Prior Authorization is recommended for benefit coverage of Zolgensma. Approval is recommended for those who meet the Criteria for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zolgensma as well as the specialized training required for administration of Zolgensma, approval requires Zolgensma to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for one dose per lifetime. For certain criteria, verification is required as noted by **[verification required by prescriber]**. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

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

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

1. **Spinal Muscular Atrophy – Treatment.** Approve for a one-time per lifetime dose if the patient meets the following criteria (A, B, C, D, E, F, G, H, I, J, K, and L):
   - **A)** Patient is less than 2 years of age; AND
   - **B)** If the patient is a premature neonate, full-term gestational age of 39 weeks and 0 days has been met; AND
   - **C)** Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene reported as at least one of the following: homozygous deletion, homozygous mutation, or compound heterozygous mutation **[documentation required]**; AND
   - **D)** Patient meets one of the following (i or ii):
     - **i.** Patient has three or fewer survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR
     - **ii.** Patient meets the following (a and b):
       - **a)** Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND
       - **b)** The number of survival motor neuron 2 (SMN2) gene copies has been determined by a quantitative assay capable of distinguishing between four SMN2 gene copies and five or greater SMN2 gene copies; AND
   - **E)** Patient has started or will receive systemic corticosteroids equivalent to oral prednisolone at a dose of 1 mg/kg per day commencing 1 day prior to Zolgensma infusion and for a total of 30 days; AND
   - **F)** Baseline anti-AAV9 antibody titers are ≤ 1:50; AND
   - **G)** The following laboratory tests will be evaluated prior to administration of Zolgensma (i, ii, iii, and iv):
     - **i.** Baseline liver function testing; AND
       Note: Examples of tests include aspartate aminotransferase, alanine aminotransferase, total bilirubin, prothrombin time.
     - **ii.** Creatinine; AND
     - **iii.** Complete blood count, including hemoglobin and platelet counts; AND
     - **iv.** Troponin-I levels; AND
   - **H)** Patient has not received Zolgensma in the past **[verification required by prescriber]**; AND
     Note: Verify through claims that the patient has not previously received Zolgensma AND, if no claim for Zolgensma is present, the prescriber must attest that the patient has not previously received Zolgensma.
   - **I)** For a patient currently receiving or who has received prior treatment with Spinraza (nusinersen injection for intrathecal use), the prescriber attests that further therapy with Spinraza will be discontinued; AND
   - **J)** For a patient currently receiving or who has received prior treatment with Evrysdi (risdiplam oral solution), the prescriber attests that further therapy with Evrysdi will be discontinued; AND

K) Medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND

L) If criteria A through K are met, approve one dose (kit) of Zolgensma based on the current weight in kg (within the past 14 days) **[documentation required]** per the cited NDC as in Table 2 below.

Table 2. Dose of Zolgensma Based on Availability.[1]

Patient Weight Range (kg)	Dose Volume (mL)*	Zolgensma Kit Configuration			NDC Number
		5.5 mL vial	8.3 mL vial	Total Vials per Kit	
2.6 to 3.0	16.5	0	2	2	71894-120-02
3.1 to 3.5	19.3	2	1	3	71894-121-03
3.6 to 4.0	22.0	1	2	3	71894-122-03
4.1 to 4.5	24.8	0	3	3	71894-123-03
4.6 to 5.0	27.5	2	2	4	71894-124-04
5.1. to 5.5	30.3	1	3	4	71894-125-04
5.6 to 6.0	33.0	0	4	4	71894-126-04
6.1 to 6.5	35.8	2	3	5	71894-127-05
6.6 to 7.0	38.5	1	4	5	71894-128-05
7.1 to 7.5	41.3	0	5	5	71894-129-05
7.6 to 8.0	44.0	2	4	6	71894-130-06
8.1 to 8.5	46.8	1	5	6	71894-131-06
8.6 to 9.0	49.5	0	6	6	71894-132-06
9.1 to 9.5	52.3	2	5	7	71894-133-07
9.6 to 10.0	55.0	1	6	7	71894-134-07
10.1 to 10.5	57.8	0	7	7	71894-135-07
10.6 to 11.0	60.5	2	6	8	71894-136-08
11.1 to 11.5	63.3	1	7	8	71894-137-08
11.6 to 12.0	66.0	0	8	8	71894-138-08
12.1 to 12.5	68.8	2	7	9	71894-139-09
12.6 to 13.0	71.5	1	8	9	71894-140-09
13.1 to 13.5	74.3	0	9	9	71894-141-09
≥ 13.6 kg†	Refer to the medical director for approval of specific NDCs				

* Dose volume is calculated using the upper limit of the patient weight range for pediatric patients less than 2 years of age between 2.6 kg and 13.5 kg; † Dose volume for pediatric patients less than 2 years of age weighing equal to or greater than 13.6 kg will require a combination of Zolgensma kits.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zolgensma is not recommended in the following situations:

1. **Patient has Complete Paralysis of All Limbs.** This is cited as a limitation of use in the Zolgensma prescribing information.[1] Data are needed to determine if this patient population would derive benefits from Zolgensma.

2. **Patient has Permanent Ventilator Dependence.** This is cited as a limitation of use in the Zolgensma prescribing information.[1] Data are needed to determine if this patient population would derive benefits from Zolgensma.

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

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NA – Not applicable.