PRIOR AUTHORIZATION POLICY

POLICY: Spinal Muscular Atrophy – Gene Therapy – Zolgensma Prior Authorization Policy

- Zolgensma® (onasemnogene abeparvovec-xioi intravenous infusion – Novartis)

REVIEW DATE: 10/30/2024

OVERVIEW

Zolgensma, an adeno-associated virus vector-based gene therapy, is indicated for the treatment of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene in patients who are less than 2 years of age.[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. The phenotypic expression of the disease is impacted by the survival motor neuron 2 (SMN2) gene copy number. 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. Of note, various motor ability assessments are used in clinical practice to characterize functional impairment in spinal muscular atrophy. Different function motor scales are utilized to evaluate patients. When motor neuron function is lost, it cannot be regained, which greatly impacts patients who have experienced progression (e.g., patients with complete paralysis of limbs or permanent ventilator dependence).

Table 1. Types of Spinal Muscular Atrophy.[5]

* Without disease-modifying treatment or mechanical ventilation; 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 are some 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. Other information is available in older adults. 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, standing without assistance). 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 scores, ventilator use). In general, patients who received Zolgensma experienced better outcomes compared with what would normally be anticipated without treatment. Other data are also available regarding Zolgensma.[10-15]

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 are 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/kg of body weight per day for a total of 30 days. Prior to administration of Zolgensma, evaluate creatinine and complete blood counts. 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 ≤ 1:50.

POLICY STATEMENT

Prior Authorization is recommended for prescription 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 a physician who has consulted with or who specializes in the condition. All approvals are provided for one-time (per lifetime) as a single dose. The approval duration is 1 month to allow for an adequate timeframe to prepare and administer one dose of therapy. For the dosing criteria, verification of the appropriate weight-based dosing is required by a Medical Director as noted by **[verification required]**. If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. 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 results, medical test results, claims records, prescription receipts, 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) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O):
   - **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
     Note: Full-term gestational age can be defined as the postmenstrual age (gestational age plus chronological age) being equal to ≥ 39 weeks and 0 days.
   - **C)** Patient has not received Zolgensma in the past **[verification in claims history required]**; AND
     Note: If no claim for Zolgensma is present (or if claims is not available), the prescribing physician confirms that the patient has not previously received Zolgensma.

D) Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 (SMN1) gene **[documentation required]**; AND
Note: Pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations.

E) 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 BOTH of the following (a and b):
  - **a)** Patient has four SMN2 gene copies **[documentation required]**; AND
  - **b)** The number of 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

F) According to the prescribing physician, 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 for a total of 30 days; AND

G) Baseline anti-AAV9 antibody titers are ≤ 1:50 **[documentation required]**; AND

H) Patient has undergone liver function testing within the past 30 days and meets ALL of the following (i, ii, iii, and iv):
- **i.** Alanine aminotransferase levels are ≤ 2 times the upper limit of normal **[documentation required]**; AND
- **ii.** Aspartate aminotransferase levels are ≤ 2 times the upper limit of normal **[documentation required]**; AND
- **iii.** Total bilirubin levels are ≤ 2 times the upper limit of normal **[documentation required]**; AND
  Note: Patient with elevated bilirubin levels due to neonatal jaundice are acceptable.
- **iv.** Prothrombin time results are ≤ 2 times the upper limit of normal **[documentation required]**; AND

I) Patient has undergone a renal function assessment within the past 30 days and has a creatinine level < 1.0 mg/dL **[documentation required]**; AND

J) A complete blood count has been obtained within the past 30 days and the patient meets BOTH of the following (i and ii):
- **i.** White blood cell count is ≤ 20,000 cells per mm^3 **[documentation required]**; AND
- **ii.** Hemoglobin levels are between 8 g/dL and 18 g/dL **[documentation required]**; AND

K) For a patient currently receiving or who has received prior treatment with Spinraza (nusinersen intrathecal injection), the prescribing physician confirms that further therapy with Spinraza will be discontinued; AND

L) For a patient currently receiving or who has received prior treatment with Evrysdi (risdiplam oral solution), the prescribing physician confirms that further therapy with Evrysdi will be discontinued; AND

M) 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

N) Current patient body weight has been obtained within the past 14 days **[documentation required]**; AND

O) If criteria A through N are met, approve one dose of Zolgensma to provide for a one-time (per lifetime) single dose of 1.1×10^{14} vector genomes per kg (vg/kg) of body weight by intravenous infusion **[verification required]**. Zolgensma is provided as a customized kit to meet dosing requirements for each patient per their weight (in kilograms). Zolgensma kit sizes (per the cited NDC) are in Table 2.

Table 2. Zolgensma Kit Sizes.[1]
† Vial nominal concentration is 2.0 x 10^{13} vg/mL and contains an extractable volume of not less than 5.5 mL; ˚ Vial nominal concentration is 2.0 x 10^{13} vg/mL and contains an extractable volume of not less than 8.3 mL.

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. **Administration to Individuals In Utero.** Zolgensma is not approved for in utero administration per the prescribing information.

4. **Prior Receipt of Gene Therapy.** Zolgensma has not been studied in patients who previously received gene therapy.

5. 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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