UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Spinal Muscular Atrophy – Gene Therapy – Zolgensma Utilization Management Medical Policy

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

REVIEW DATE: 10/01/2025

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 < 2 years of age.[1]

Limitations of use: 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, progressive, neuromuscular disorder caused by biallelic deletions or pathogenic variants in the SMN1 gene which can be identified by genetic testing.[3-6] The subsequent reduced levels of survival motor neuron (SMN) protein impacts brainstem and spinal cord motor neurons. The estimated incidence in the US in one in 11,000.[4] The phenotypic expression of the disease is generally impacted by the survival motor neuron 2 (SMN2) gene copy number.[3-5] Patients with a higher number of SMN2 gene copies often have less severe disease with milder progression. Table 1 describes disease types. Of note, various motor ability assessments and different functional motor scales are used in clinical practice to characterize impairment in patients with spinal muscular atrophy. 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.[5,6]

	Age at Onset	Features/Clinical Presentation*	Lifespan*	SMN2 Gene Copy Number
Type 0 (< 1% of patients)	Birth	Severe hypotonia and weakness with respiratory failure at birth. There is no achievement of motor milestones.	A few weeks to days (< 6 months)	1
Type 1 (50% of patients)	< 6 months	Poor muscle tone and lack of movement. Respiratory assistance may be needed. Patients are never able to sit without support.	< 2 years	1 to 2 for 80% of patients
Type 2 (30% of patients)	6 to 18 months	Patients are able to sit. However, patients are unable to walk or stand without assistance.	Close to normal	2 to 3 for over 90% of patients
Type 3 (10% to 20% of patients)	≥ 18 months	Walks independently but may lose this ability as the disease progresses. There is loss of motor skills.	Normal	3 to 5 for most patients
Type 4 (< 1% of patients)	> 18 years	Independent walking. Fatigue and proximal muscle weakness.	Normal	4 for 75% of patients; 5 or 6 for 25% of patients

* With supportive care only; SMN2 – Survival motor neuron 2.

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.[1,7-12] One trial was an open-label, single-arm study (STR1VE [n = 21])[9] and the other was an open-label, single-arm, ascending-dose clinical trial (START [n = 15] {12 patients received a therapeutic dose}).[1,7,8] 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.[13]

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.[14] 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.[14] 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.[15] 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.

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. 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 medical benefit coverage of Zolgensma. Approval is recommended for those who meet the **Criteria** and **Dosing** 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 30 days 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 for the use of Zolgensma as 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. All documentation must include patient-specific identifying information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

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1. **Spinal Muscular Atrophy – Treatment.** Approve for a one-time (per lifetime) single dose if the patient meets the following (A, B, C, D, E, G, H, I, J, K, L, M, and N):
   - **A)** Patient is < 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 history 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)** Baseline anti-AAV9 antibody titers are ≤ 1:50 **[documentation required]**; AND
   - **G)** 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

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

I) 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

J) 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

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

L) The 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

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

N) If criteria A through M are met, approve one dose of Zolgensma to provide for a one-time (per lifetime) single dose of 1.1 x 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.

Dosing. The recommended dose of Zolgensma is one-time (per lifetime) as a single-dose intravenous infusion of 1.1 x 10^{14} vector genomes (vg)/kg based on the current patient weight in kg (within the past 14 days). Zolgensma is provided as a customized kit to meet dosing requirements for each patient per their weight (in kilograms). Refer to the appropriate NDC number below for approval.

Table 2. Zolgensma Kit Sizes.[1]

Patient Weight Range (kg)	Zolgensma Kit Sizes			NDC Number
	5.5 mL vial†	8.3 mL vial˚	Total Vials per Kit	
2.6 to 3.0	0	2	2	71894-120-02
3.1 to 3.5	2	1	3	71894-121-03
3.6 to 4.0	1	2	3	71894-122-03
4.1 to 4.5	0	3	3	71894-123-03
4.6 to 5.0	2	2	4	71894-124-04
5.1. to 5.5	1	3	4	71894-125-04
5.6 to 6.0	0	4	4	71894-126-04
6.1 to 6.5	2	3	5	71894-127-05
6.6 to 7.0	1	4	5	71894-128-05
7.1 to 7.5	0	5	5	71894-129-05
7.6 to 8.0	2	4	6	71894-130-06
8.1 to 8.5	1	5	6	71894-131-06
8.6 to 9.0	0	6	6	71894-132-06
9.1 to 9.5	2	5	7	71894-133-07
9.6 to 10.0	1	6	7	71894-134-07
10.1 to 10.5	0	7	7	71894-135-07
10.6 to 11.0	2	6	8	71894-136-08
11.1 to 11.5	1	7	8	71894-137-08
11.6 to 12.0	0	8	8	71894-138-08
12.1 to 12.5	2	7	9	71894-139-09
12.6 to 13.0	1	8	9	71894-140-09
13.1 to 13.5	0	9	9	71894-141-09
13.6 to 14.0	2	8	10	71894-142-10
14.1 to 14.5	1	9	10	71894-143-10
14.6 to 15.0	0	10	10	71894-144-10
15.1 to 15.5	2	9	11	71894-145-11
15.6 to 16.0	1	10	11	71894-146-11
16.1 to 16.5	0	11	11	71894-147-11
16.6 to 17.0	2	10	12	71894-148-12
17.1 to 17.5	1	11	12	71894-149-12
17.6 to 18.0	0	12	12	71894-150-12
18.1 to 18.5	2	11	13	71894-151-13
18.6 to 19.0	1	12	13	71894-152-13
19.1 to 19.5	0	13	13	71894-153-13
19.6 to 20.0	2	12	14	71894-154-14
20.1 to 20.5	1	13	14	71894-155-14
20.6 to 21.0	0	14	14	71894-156-14

† 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 with advanced spinal muscular atrophy 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 with advanced spinal muscular atrophy 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.

REFERENCES

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15. Glascock J, Sampson J, Connolly AM, et al. Revised recommendations for the treatment of infants diagnosed with spinal muscular atrophy via newborn screening who have 4 copies of SMN2. *J Neuromuscul Dis*. 2020;7(2):97-100.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	For Spinal Muscular Atrophy, regarding the requirement which mandates that a premature neonate to reach full term gestational age of 39 weeks and 0 days, a Note was added that full-term gestational age can be defined as the postmenstrual age (gestational age plus chronological age) being equal to ≥ 39 weeks and 0 days.	11/01/2023
Annual Revision	The Policy Statement was clarified to add that all approvals are provided for one-time (per lifetime) as a single dose. A sentence was added that for the dosing criteria, verification of the appropriate weight-based dosing is required by a Medical Director as noted by **[verification required]**. The phrase "if claims history is available" was added regarding that verification in claims history is required for certain criteria. Regarding Documentation, "medical test results" and "prescription receipts" were added; laboratory "tests" was changed to "results". In addition, the following changes were made: **Spinal Muscular Atrophy – Treatment:** • For approval, the word "single" was added before the word "dose" for clarification. The phrase "per lifetime" was placed in parenthesis. • Regarding the Note in the criteria which addresses that the patient has not received Zolgensma (with verification in claims history required), a phrase was added to include situations in which claims history is not available. • The phrase "liver function assessment" was replaced with "liver function testing". • In phrases in which a requirement is "within the last 30 days", the word "last" was replaced with "past". • The criterion regarding a current patient body weight be obtained within the past 14 days was moved to a separate criterion. Previously, this requirement was combined with the Dosing. • Dosing was clarified with emphasis that Zolgensma is given as a one-time (per lifetime) single dose. Also, "documentation required" was replaced with "verification required". **Conditions Not Recommended for Approval:** The condition of "Prior Receipt of Gene Therapy" was added.	10/30/2024
Annual Revision	**Spinal Muscular Atrophy – Treatment:** The requirement was removed which stated that according to the prescribing physician, the 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. Also, regarding the requirement that addresses Evrysdi, it was added that the agent is now available in tablets.	10/01/2025