Drug Coverage Policy

Effective Date.....04/15/2024
Coverage Policy Number.....IP0185

Spinal Muscular Atrophy – Gene Therapy – Zolgensma

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

INSTRUCTIONS FOR USE
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Medical Necessity Criteria

Gene Therapy coverage varies across plans. Refer to the customer's benefit plan document for coverage details.

Zolgensma is considered medically necessary when the following criteria are met:

1. **Spinal Muscular Atrophy – Treatment.** Individual meets **ALL** of the following criteria:
   A. **BOTH** of the following:
      i. Less than 2 years of age
      ii. If premature neonate, full-term gestational age has been met

B. Documentation of **BOTH** of the following:
    i. Genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 (*SMN1*) gene
    ii. **ONE** of the following:
        a. Three or fewer survival motor neuron 2 (*SMN2*) gene copies
        b. **BOTH** of the following:
            (1) Four survival motor neuron 2 (*SMN2*) gene copies
            (2) 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
C. Documentation of **ALL** of the following prior to the administration of Zolgensma:
    i. Baseline anti-AAV9 antibody titers are less than or equal to 1:50
    ii. Liver function assessment within the last 30 days demonstrating **ALL** of the following:
        a. Alanine aminotransferase levels are no greater than 2 times the upper limit of normal
        b. Aspartate aminotransferase levels are no greater than 2 times the upper limit of normal
        c. Total bilirubin levels are no greater than 2 times the upper limit of normal

            Elevated bilirubin levels due to neonatal jaundice are acceptable

        d. Prothrombin results are no greater than 2 times the upper limit of normal
    iii. Renal functions assessment within the last 30 days demonstrating a creatinine level of less than 1.0 mg/dL
    iv. Complete blood count within the last 30 days demonstrating **BOTH** of the following:
        a. White blood cell count no greater than 20,000 cells/mm^3
        b. Hemoglobin levels between 8 g/dL and 18 g/dL
D. Prescriber attests that prophylactic systemic corticosteroids, equivalent to oral prednisolone at a dose of 1 mg/kg per day, will commence 1 day prior to Zolgensma infusion and will continue daily for a total of 30 days
E. No previous use of onasemnogene abeparvovec-xioi (Zolgensma)
F. If currently receiving, or has received, treatment with Spinraza® (nusinersen injection for intrathecal use), the physician attests that further therapy with Spinraza will be discontinued
G. If currently receiving, or has received, treatment with Evrysdi® (risdiplam oral solution), the physician attests that further therapy with Evrysdi will be discontinued
H. **BOTH** of the following:
    i. Submission of medical records (including, but not limited to): chart notes (including developmental motor milestones), laboratory data, genetic testing results
    ii. Agreement to share required plan specific treatment outcome measures
I. 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

Dosing. A single intravenous infusion of Zolgensma at a dose of 1.1 x 1014 vector genomes (vg)/kg based on the individual's current (within the past 14 days) weight in kilograms (kg). Zolgensma is provided as a customized kit to meet dosing requirements for each individual per their documented weight (in kilograms). Configuration of the dose-kit is located in the Background Dosing section.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Authorization Duration

Authorization is for a one-time treatment for a one month duration or until 2 years of age, whichever comes first.

Conditions Not Covered

Any other use is considered not medically necessary, including the following (this list may not be all inclusive):

1. **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. **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.

Background

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
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. Trials are ongoing in older adults, as well as 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 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 x 1014 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.

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 to 14.0	77.0	2	8	10	71894-142-10
14.1 to 14.5	79.8	1	9	10	71894-143-10
14.6 to 15.0	82.5	0	10	10	71894-144-10
15.1 to 15.5	85.3	2	9	11	71894-145-11
15.6 to 16.0	88.0	1	10	11	71894-146-11
16.1 to 16.5	90.8	0	11	11	71894-147-11
16.6 to 17.0	93.5	2	10	12	71894-148-12
17.1 to 17.5	96.3	1	11	12	71894-149-12
17.6 to 18.0	99.0	0	12	12	71894-150-12
18.1 to 18.5	101.8	2	11	13	71894-151-13
18.6 to 19.0	104.5	1	12	13	71894-152-13
19.1 to 19.5	107.3	0	13	13	71894-153-13
19.6 to 20.0	110.0	2	12	14	71894-154-14
20.1 to 20.5	112.8	1	13	14	71894-155-14
20.6 to 21.0	115.5	0	14	14	71894-156-14

* 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 21.0 kg.

References

1. Zolgensma intravenous infusion [prescribing information]. Bannockburn, IL: Novartis; October 2023.
2. ACOG Committee Opinion No 579: Definition of term pregnancy. *Obstet Gynecol*. 2013;122(5):1139-1140.
3. Arnold ES, Fischbeck KH. Spinal muscular atrophy. *Handb Clin Neurol*. 2018;148:591-601.
4. Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. 2000 Feb 24 [Updated 2020 December 3]. In: Adam MP, Ardinger, HH, Pagon RA, et al, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1352/. Accessed on November 1, 2023.
5. Nicolau S, Waldrop MA, Connolly AM, Mendell JR. Spinal muscular atrophy. *Semin Pediatr Neurol*. 2021;37:100878.
6. Yeo CJJ, Darras BT. Overturning the paradigm of spinal muscular atrophy as just a motor neuron disease. *Pediatr Neurol*. 2020;109:12-19.
7. Spinraza intrathecal injection [prescribing information]. Cambridge, MA: Biogen; February 2023.
8. Evrysdi oral solution [prescribing information]. South San Francisco, CA: Genentech/Roche; October 2023.
9. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene replacement therapy for spinal muscular atrophy. *N Engl J Med*. 2017;377(18):1713-1722.
10. Mendell JR, Al-Zaidy SA, Lehman KJ, et al. Five-year extension results of the Phase I START trial of onasemnogene abeparvovec in spinal muscular atrophy. *JAMA Neurol*. 2021;78(7):834-841.
11. Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicenter, phase 3 trial. *Lancet Neurol*. 2021;20:284-293.
12. Strauss KA, Farrar MS, Muntoni F, et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial. *Nat Med*. 2022;28:1390-1397.
13. Strauss KA, Farrar MS, Muntoni F, et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial. *Nat Med*. 2022;28:1381-1389.
14. Mercuri E, Muntoni F, Baranello G, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy type 2 (STR1VE-EU): an open-label, single-arm, multicenter, phase 3 trial. *Lancet Neurol*. 2021;20:832-841.
15. Blair HA. Onasemnogene abeparvovec: a review of spinal muscular atrophy. *CNS Drugs*. 2022;36:995-1005.
16. Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. *J Neuromuscul Dis*. 2018;5:145-158.
17. 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.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	• Updated coverage policy title. • Removed coding information from policy.	04/15/2024

The policy effective date is in force until updated or retired.