POLICY: Spinal Muscular Atrophy – Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion – AveXis)

DATE REVIEWED: 06/03/2020

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. The use of Zolgensma in patients with advanced spinal muscular atrophy (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been assessed. The recommended dose of Zolgensma is 1.1 x 10^{14} vector genomes (vg) per kg of body weight. 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. 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.[1] The definition of a full-term pregnancy commences at 39 weeks and 0 days gestation.[2]

Disease Overview

Spinal muscular atrophy is a rare, genetic, autosomal recessive neuromuscular disorder caused by deletions or mutations in the SMN1 gene which creates survival motor neuron (SMN) protein that is essential for proper motor neuron development.[3,4] The carrier frequency is around 1 in 50 people and the condition incidence is approximately 1 in 10,000 live births.[5] Spinal muscular atrophy is a heterogeneous condition characterized by the degeneration and loss of lower motor neurons, which causes muscle atrophy.[3,4,7-9] Five main disease subtypes have been identified (Types 0 through 4). The classification is determined primarily by the age of onset and achievement of developmental milestones. Patients with multiple copies of the survival motor neuron 2 (SMN2) gene have a decrease in disease severity because some functional SMN protein is produced. Type 0 spinal muscular atrophy is the most severe subtype and impacts infants before birth with death resulting before the patient is 6 months of age. Type 1 spinal muscular atrophy is the most common severe disease form with an age of onset between birth and 6 months of age. Without treatment, patients are unable to sit and death occurs before the patient is 2 years of age. Patients with Type 2 disease usually have disease onset before 18 months of age and generally do not achieve the ability to stand or walk without assistance. However, lifespan generally exceeds 2 years of age. Type 3 disease has a variable onset sometime after 18 months of age. The lifespan is normal but patients may lose the ability to walk in adulthood. Type 4 disease usually manifests in adulthood and the disease course is generally very mild with proximal muscle weakness. The disease types are described in Table 1.

Table 1. Types of Spinal Muscular Atrophy.[3,4,7]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Copy Gene Number
0	Prenatal	Minimal functioning, respirator required at birth.	< 6 months	0 to 1
1	< 6 months	Poor muscle tone, lack of movement, respiratory assistance needed. Patients are never able to sit.	< 2 years	1 to 3
2	6 to 18 months	Patients are able to sit. However, patients are unable to walk or stand without assistance.	10 to 40 years	2 to 3

Table 1 (continued). Types of Spinal Muscular Atrophy.[3,4,7]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Copy Gene Number
3	> 18 months	Walks independently but may lose this ability as the disease progresses.	Adulthood	3 to 4
4	Adolescence to adulthood	Walk until adulthood.	Normal lifespan	≥ 4

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

Clinical Efficacy

The efficacy of Zolgensma was established in patients less than 2 years of age with spinal muscular atrophy who had bi-allelic mutations in the SMN1 gene.[1,5] One trial was an open-label, single-arm study which is ongoing and the other was an open-label, single-arm, ascending-dose clinical trial.[1] 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 at 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.[1,5] 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] Additional data supports benefits in patients in the high-dose cohort.[10-12]

Guidelines

In 2018, a working group comprised 15 experts developed a treatment algorithm for infants with spinal muscular atrophy.[6] A key recommendation was that for infants with two or three SMN2 gene copies, immediate treatment should be administered. For patients with four or more SMN2 gene copies, it is recommended to monitor patients and treat at symptom onset.

Safety

Zolgensma has a Boxed Warning regarding acute serious liver injury.[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. Also, temporary increases in cardiac troponin-I levels were noted with Zolgensma administration. Therefore, assess troponin-I prior to the infusion. 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 benefit coverage of Zolgensma. Approval is recommended for those who meet the Criteria for the listed indication(s). Because of the 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. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

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 Zolgensma is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Spinal Muscular Atrophy (SMA).** Approve for a one-time dose if the patient meets the following criteria (A, B, C, D, E, F, G, H, I, J and K):
   - **A)** The 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)** The 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)** The patient has three or fewer survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND
   - **E)** 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; 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, and iii):
     - **i.** Baseline liver function testing (e.g., asparatate aminotransferase, alanine aminotransferase, total bilirubin, prothrombin time); AND
     - **ii.** Platelet counts; AND
     - **iii.** Troponin-I levels; AND
   - **H)** 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
   - **I)** The patient has not received Zolgensma in the past; AND
   - **J)** For patients who have received prior treatment with Spinraza (nusinersen injection for intrathecal use) further therapy with Spinraza will be discontinued; AND
   - **K)** If criteria A through J are met, approve one dose (kit) of Zolgensma based on the current (within the past 14 days kg weight **[documentation required]** per the cited NDC as in Table 2 below.

Dosing. The recommended dose of Zolgensma for single-dose intravenous infusion is 1.1×10^{14} vector genomes (vg)/kg. Zolgensma is provided as a customized kit to meet dosing requirements for each patient. Refer to the appropriate NDC number below for approval. For patients < 2 years of age who weight ≥ 13.6 kg, refer to the Medical Director for approval of specific NDC kits.

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 < 2 years of age between 2.6 kg and 13.65 kg; † Dose volume for pediatric patient < 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

Zolgensma 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. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **The patient has four or more survival motor neuron 2 (SMN2) gene copies.** These patients were not studied and guidance does not recommend treatment.

2. **The patient has complete paralysis of limbs to suggest advanced spinal muscular atrophy.** 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. **The patient has permanent ventilator dependence to suggest advanced spinal muscular atrophy.** 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.

4. Coverage is not recommended for circumstances not listed in the Authorization Criteria (FDA-approved indications and Other Uses with Supportive Evidence). Criteria will be updated as new published data are available.

REFERENCES

1. Zolgensma® suspension for intravenous infusion [prescribing information]. Bannockburn, IL: AveXis; May 2019.
2. ACOG Committee Opinion No 579: Definition of term pregnancy. *Obstet Gynecol*. 2013;122(5):1139-1140.
3. Nash LA, Burns JK, Chardon JW, et al. Spinal muscular atrophy: more than a disease of motor neurons? *Curr Mol Med*. 2016;16(9):779-792.
4. Arnold ES, Fischbeck KH. Spinal muscular atrophy. *Handb Clin Neurol*. 2018;148:591-601.
5. 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.
6. Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. *J Neuromuscular Dis*. 2018;5:145-158.
7. Carre A, Empey C. Review of spinal muscular atrophy (SMA) for prenatal and pediatric genetic counselors. *J Genet Counsel*. 2016;25:32-43.
8. Mercuri E, Rinkel RS, Muntoni F, et al, for the SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord*. 2018;28(2):103-115. Available at: https://air.unimi.it/retrieve/handle/2434/702816/1424447/main.pdf. Accessed on June 4, 2020.
9. Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. 2000 Feb 24 [Updated 2019 Nov 14]. In: Adam MP, Ardinger, HH, Pagon RA, et al, editors. GeneReviews® [Intermet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1352/. Accessed on May 19, 2020.
10. Al-Zaidy SA, Kolb SJ, Lowes L, et al. AVXS-101 (onasemnogene abeparvovec) for SMA1: comparative study with a prospective natural history cohort. *J Neuromuscul Dis*. 2019;6(3):307-317.
11. Al-Zaidy SA, Pickard AS, Kotha K, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. *Pediatr Pulmonol*. 2019;54:179-185.
12. Lowes LP, Alfano LN, Arnold WD, et al. Impact of age and motor function in a Phase 1/2A study of infants with SMA Type 1 receiving single-dose gene replacement therapy. *Pediatric Neurol*. 2019;98:39-45.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New policy	Not applicable	05/24/2019
Selected revision	**1. Spinal Muscular Atrophy, Treatment:** A documentation requirement was added in the criterion that requires that the patient has three or fewer survival motor neuron 2 (SMN2) gene copies. Regarding the laboratory tests criteria, the wording was changed from "assessments have been completed or will be performed" to "tests will be evaluated". A criterion was added that for patients who have received prior treatment with Spinraza® (nusinersen injection for intrathecal use) further therapy with Spinraza will be discontinued. **2. Conditions Not Recommended for Approval:** The criterion that does not approve Zolgensma for patients with complete paralysis of limbs and/or permanent ventilator dependence was split into two different criteria. The criterion in this section stating to not approve if the patient is currently receiving Spinraza was deleted as this is addressed in the approval conditions above.	06/18/2019
Annual revision	The following changes was made: **1. Spinal Muscular Atrophy:** Criteria were added that if the patient is a premature neonate, full term gestational age of 39 weeks and 0 days has been met.	06/03/2020