Drug and Biologic Coverage Policy

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Coverage Policy Number 1904

Onasemnogene Abeparvovec-xioi (Zolgensma®)

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Genetic Testing for Hereditary and Multifactorial Conditions
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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for onasemnogene abeparvovec-xioi (Zolgensma®)

Coverage Policy

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

Onasemnogene Abeparvovec-xioi (Zolgensma®) is considered medically necessary when ALL of the following criteria are met:

- Individual is less than 2 years of age
- If individual is a premature neonate, full-term gestational age has been met
- Documentation of diagnosis of SMA confirmed by the following:
  - bi-allelic pathogenic or likely pathogenic variants in the survival motor neuron 1 (*SMN1*) gene
- Documentation of three or fewer spinal motor neuron 2 (*SMN2*) gene copies
- Individual 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
- Documentation of baseline anti-AAV9 antibody titers are ≤ 1:50

- Documentation of baseline laboratory assessments consisting of ALL of the following
    - liver function testing (for example, aspartate aminotransferase, alanine aminotransferase, total bilirubin, prothrombin time);
    - Platelet counts
    - Troponin-I or T levels
- 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
- For individuals who have received prior treatment with Spinraza® (nusinersen injection for intrathecal use), the health care professional attests that further therapy with Spinraza will be discontinued
- For individuals who have received prior treatment with Evrysdi® (risdiplam oral solution), the health care professional attests that further therapy with Evrysdi will be discontinued
- No previous use of Onasemnogene Abeparvovec-xioi (Zolgensma)
- Submission of medical records including, but not limited to chart notes (including developmental motor milestones), laboratory data, and genetic testing results
- Agreement to share required plan specific treatment outcome measures

Onasemnogene Abeparvovec-xioi (Zolgensma®) is considered experimental, investigational, or unproven for all other indications including the following:

- Individuals having four or more spinal motor neuron 2 (*SMN2*) gene copies
- Individuals with complete paralysis of limbs (for example documented with CHOP-INTEND score or age-appropriate motor skills examination instrument)
- Individuals requiring permanent ventilator use where permanent ventilation is defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in the absence of an acute reversible illness, excluding perioperative ventilation
- Individuals with advanced spinal muscular atrophy
- Administration to individuals in-utero
- Repeat administration within lifetime

When above criteria are met, a one-time authorization of one dose (kit) of Abeparvovec-xioi (Zolgensma®) per lifetime will be made based upon documented weight (in kilograms) per the dose – kit configuration in the Recommended Dosing Section - Appendix

Authorization is for a one-time treatment for a one month's duration or until the age of 2 whichever comes first.

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.

Documentation: When documentation is required, the prescriber must provide written documentation supporting the trials of these other agents. Documentation may include, but is not limited to, chart notes, prescription claims records, and/or prescription receipts.

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.[1] 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 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 survival motor neuron 2 (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 main 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 Copy Gene 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 lifespan	≥ 4

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

Besides Zolgensma, other therapies are available. **Spinraza®** (nusinersen injection for intrathecal use), 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. Trials are evolving with Spinraza in adults. Data are also available in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy.

Evrysdi® (risdiplam oral solution), a SMN2 splicing modifier, is indicated for the treatment of spinal muscular atrophy in patients 2 months of age and older.[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 established in patients less than 2 years of age with spinal muscular atrophy who had bi-allelic mutations in the SMN1 gene.[1,9] 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.[1,9] 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] Additional data supports benefits in patients in the high-dose cohort.[10-12]

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.[13] 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.[13] 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.[14] 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.

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[†]	Individual clinical review required to configure dosing be used				

[*] 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.

Use in Special Populations

Administration of Zolgensma to premature neonates before reaching full-term gestational age is not recommended, because concomitant treatment with corticosteroids may adversely affect neurological development. Delay Zolgensma infusion until the corresponding full-term gestational age is reached.

The safety of Zolgensma was studied in pediatric patients who received Zolgensma infusion at age 0.3 to 7.9 months (weight range 3.0 kg to 8.4 kg).

The efficacy of Zolgensma was studied in pediatric patients who received Zolgensma infusion at age 0.5 to 7.9 months (weight range 3.6 kg to 8.4 kg).

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, 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 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 ≤ 1:50.

Coding/ Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J3399	Injection, Onasemnogene abeparvovec-xioi, per treatment, up to 5 x 10^{15} vector genomes

References

1. Arnold ES, Fischbeck KH. Spinal muscular atrophy. Handb Clin Neurol. 2018;148:591-601.
2. Carre A, Empey C. Review of spinal muscular atrophy (SMA) for prenatal and pediatric genetic counselors. J Genet Counsel. 2016;25:32-43.
3. 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.
4. 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.
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. Zolgensma® suspension for intravenous infusion [prescribing information]. Bannockburn, IL: AveXis; May 2019.