

Clinical Policy: Onasemnogene Abeparvovec (Zolgensma)

Reference Number: PA.CP.PHAR.421

Effective Date: 01/2020

Last Review Date: 04/2025

Description

Onasemnogene abeparvovec (Zolgensma[®]) is an adeno-associated virus (AAV) vector-based gene therapy.

FDA Approved Indication(s)

Zolgensma is indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in survival motor neuron 1 (SMN1) gene.

Limitation(s) of use:

- The safety and effectiveness of repeat administration of Zolgensma have not been evaluated.
- The use of Zolgensma in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness[®] that Zolgensma is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Spinal Muscular Atrophy (must meet all):

1. Diagnosis of SMA;
2. Genetic testing confirms the presence of one of the following (a, b, or c):
 - a. Homozygous deletions of SMN1 gene (e.g., absence of the SMN1 gene);
 - b. Homozygous mutation in the SMN1 gene (e.g., biallelic mutations of exon 7);
 - c. Compound heterozygous mutation in the SMN1 gene (e.g., deletion of SMN1 exon 7 (allele 1) and mutation of SMN1 (allele 2));
3. Prescribed by or in consultation with a neurologist;
4. Age < 2 years;
5. Documentation of one of the following baseline scores (*see Appendix D*) (a or b):
 - a. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder (CHOP-INTEND) score;
 - b. Hammersmith Infant Neurological Examination (HINE) Section 2 motor milestone score;
6. Documentation of both of the following (a and b):
 - a. Baseline laboratory tests demonstrating Anti-AAV9 antibody titers $\leq 1:50$ as determined by ELISA binding immunoassay;
 - b. Baseline liver function test, platelet counts, and troponin-I;

7. Member does not have advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence, tracheostomy);
8. Member has not been previously treated with Zolgensma;
9. Zolgensma is not prescribed concurrently with Spinraza or Evrysdi;
10. If the member is currently on Spinraza or Evrysdi, provider submits attestation of intention to discontinue prior to treatment with Zolgensma;
11. Total dose does not exceed 1.1×10^{14} vector genomes (vg) per kilogram (kg).

Approval duration: 4 weeks (one time infusion per lifetime)

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Spinal Muscular Atrophy

1. Continued therapy will not be authorized as Zolgensma is indicated to be dosed one time only **Approval duration: Not applicable**

B. Other diagnoses/indications (must meet 1 or 2):

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

- A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53;
- B.** Advanced SMA.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ELISA: enzyme-linked immunosorbent assay

FDA: Food and Drug Administration

SMA: spinal muscular atrophy

SMN: survival motor neuron

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): serious liver injury and acute liver failure

Appendix D: General Information

- SMA is an autosomal recessive genetic disorder. It is caused by mutations in the SMN1 (survival motor neuron) gene that is found on chromosome 5 (hence the name 5q-SMA). To develop SMA, an individual must inherit two faulty (deletion or mutation) SMN1 genes, one from each parent.

- There are other types of SMA that are not related to chromosome 5 or SMN. Safety and efficacy of Zolgensma in non-SMN-related SMA have not been established.
- SMN-related SMA is classified as type 1 through 4 depending on time of onset. The age of disease onset of symptoms correlates with disease severity: the earlier the age of onset, the greater the impact on motor function. Children who display symptoms at birth or in infancy typically have the lowest level of functioning (type 1). SMA onset in children (types 2 and 3), teens or adults (type 4) generally correlates with increasingly higher levels of motor function.
- SMN2 gene copy and SMA types
 - SMN2 gene copy numbers are variable in individuals with spinal muscular atrophy. Higher numbers typically correlate with less severe disease.
 - More than 95% of individuals with spinal muscular atrophy retain at least 1 copy of the SMN2 gene
 - About 80% of individuals with Type I spinal muscular atrophy have 1 or 2 copies of the SMN2 gene
 - About 82% of individuals with Type II spinal muscular atrophy have 3 copies of the SMN2 gene
 - About 96% of individuals with Type III spinal muscular atrophy have 3 or 4 copies of the SMN2 gene
- SMA Type I: onset of symptoms (e.g., hypotonia, muscle weakness, weak cry, lack of reflexes, difficulty swallowing, poor head control, round shoulder posture, inability to sit without support, tongue fasciculations, pooling secretions, poor suck and swallow reflexes, increased risk of aspiration, and failure to thrive) prior to the age of 6 months.
- Advanced SMA: complete paralysis of limbs, permanent ventilator dependence
- Permanent Ventilation: 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.
- Active infections include HIV, HBC, HCV, Zika, upper or lower respiratory tract infection, non-respiratory tract infection within 2 weeks of administration.
- The CHOP-INTEND score is a validated 16-item, 64-point scale shown to be reliable and sensitive to change over time for SMA Type 1. In a prospective cohort study of SMA type I patients (n = 34), the mean rate of decline in the CHOP-INTEND score was 1.27 points/year (95% CI 0.21-2.33, p = 0.02). A CHOP-INTEND score greater than 40 is considered a clinically meaningful change.
- The HINE Section 2 motor milestone exam is an easily performed and relatively brief standardized clinical neurological examination that is optimal for infants aged between 2 and 24 months with good inter-observer reliability. This endpoint evaluates seven different areas of motor milestone development, with a maximum score between 2-4 points for each, depending on the milestone, and a total maximum score of 26 points.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
SMA	Administer Zolgensma as a single-dose IV infusion over 60 minutes at the dose of 1.1×10^{14} vg/kg.	Once

Indication	Dosing Regimen	Maximum Dose
	One day prior to Zolgensma infusion, begin administration of systemic corticosteroids equivalent to oral prednisolone at 1mg/kg/day for a total of 30 days. Afterwards, evaluate liver function. No liver abnormalities, taper corticosteroids over the next 28 days. If liver abnormalities persist, continue systemic corticosteroids until resolution then taper over the next 28 days.	

VI. Product Availability

Zolgensma is shipped frozen in 10 mL vials with either 5.5 mL or 8.3 mL fill volumes. Each vial has a nominal concentration is 2.0×10^{13} vg/mL.

The customized kits come in differing vial quantities based on the patient's weight in kilograms as reflected within the package insert.

VII. References

1. Zolgensma Prescribing Information. Bannockburn, IL: Novartis Gene Therapies, Inc.; October 2024. Available at: : https://www.novartis.com/us-en/sites/novartis_us/files/zolgensma.pdf. Accessed January 28, 2025.
2. 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.
3. Institute for Clinical and Economic Review (ICER). Final Evidence Report – Spinraza and Zolgensma for spinal muscular atrophy: effectiveness and value. Available at: https://icer.org/wp-content/uploads/2020/10/ICER_SMA_Final_Evidence_Report_110220.pdf. Accessed January 28, 2025.
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6. Cobben JM, de Visser M, Scheffer H, et al. Confirmation of clinical diagnosis in requests for prenatal prediction of SMA type I. *J Neurol Neurosurg Psychiatry*. 1993; 56: 319-21.
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8. Darras BT, Royden Jones H Jr, Ryan MM, et al. Neuromuscular Disorders of Infancy, Childhood, and Adolescence: A Clinician's Approach. 2nd ed. London, UK: Elsevier; 2015.
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11. National Institute for Health and Care Excellence. Onasemnogene abeparvovec for treating spinal muscular atrophy. July 2021. Available at: www.nice.org.uk/guidance/hst15. Accessed January 28, 2025.
12. Kirschner J, Butoianu N, Goemans N, et al. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. *European Journal of Paediatric Neurology* 2020; 28:38-43. doi: <https://doi.org/10.1016/j.ejpn.2020.07.001>.
13. Kichula EA, Proud CM, Rarrar MA, et al. Expert recommendations and clinical considerations in the use of onasemnogene abeparvovec gene therapy for spinal muscular atrophy. *Muscle & Nerve*. 2021;64:413–427. 2021; DOI: 10.1002/mus.27363.
14. Schroth M, Deans J, Arya K, et al. Spinal muscular atrophy update in best practices: recommendations for diagnosis considerations. *Neurol Clin Pract*. 2024 Aug;14(4):e200310. doi: 10.1212/CPJ.0000000000200310.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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

Reviews, Revisions, and Approvals	Date
Policy created	01/2020
1Q 2021 annual review: updated criteria language to restrict concomitant use with Evrysdi; references reviewed and updated.	01/2021
1Q 2022 annual review: references reviewed and updated.	01/2022
2Q 2023 annual review: no significant changes; HCPCS Code added; references reviewed and updated.	04/2023
2Q 2024 annual review: no significant changes; updated boxed warnings description to “serious liver injury and acute liver failure” to align with prescriber information; references reviewed and updated.	04/2024
2Q 2025 annual review: for initial approval criteria, added option of “four copies of SMN2 gene, determined by a quantitative assay that is able to distinguish between four SMN2 gene copies and five or more SMN2 gene copies” as supported by practice guidelines; references reviewed and updated.	04/2025