

**Pharmacy Prior Authorization  
Zolgensma - Clinical Guidelines**

**Description**

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

**FDA Approved Indication**

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.

**Limitations 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.

**Guideline Criteria**

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

**Zolgensma may be approved when the following criteria are met:**

**Initial Approval Criteria**

**A. Spinal Muscular Atrophy** (must meet all):

1. Diagnosis of SMA Type I with onset of symptoms prior to 6 months of age;
2. Genetic testing confirming 1, 2, or 3 copies of SMN2 gene;
3. 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));
4. Prescribed by or in consultation with one of the following pediatric specialties or subspecialties: neurology, pulmonology, orthopedics, neonatal-perinatal medicine, clinical genetics and genomics, physical medicine and rehabilitation, neuromuscular medicine, or neurodevelopmental disabilities;
5. Member has reached full-term gestational age;
6. Age < 2 years;
7. Prescriber verified vaccine schedule has been reviewed and modified, if necessary;
8. 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;

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- b. Hammersmith Infant Neurological Examination (HINE) Section 2 motor milestone score;
9. 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;
10. Member does not have advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence, tracheostomy, non-invasive ventilation beyond the use for sleep);
11. Member has not been previously treated with Zolgensma;
12. Zolgensma is not prescribed concurrently with Spinraza®;
13. If the member is currently on Spinraza, must meet the following (a and b):
  - a. Provider must submit evidence of clinical deterioration (e.g., sustained decrease in CHOP-INTEND score over a period of 3 to 6 months);
  - b. Documentation of provider attestation of clinical deterioration and Spinraza discontinuation;
14. Member does not have an active viral infection (*see Appendix D*);
15. Prescriber will initiate therapy with systemic corticosteroids equivalent to oral prednisone dosed at 1mg/kg one day prior to infusion for a total of 30 days and continued or tapered per prescribing information based on liver function;
16. Total dose does not exceed  $1.1 \times 10^{14}$  vector genomes (vg) per kilogram (kg).

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

### Continued Therapy

1. Spinal Muscular Atrophy: Re-authorization is not permitted

### Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications
- B. Advanced SMA

### General Information

- Boxed warning(s): acute serious liver injury and elevated aminotransferases
- 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

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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.

**Dosage and Administration**

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

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Indication	Dosing Regimen	Maximum Dose
	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.	

**References**

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