RXADVANCE
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| **Clinical Policy Title:** | onasemnogene abeparvovec |
| **Policy Number:** | RxA.577 |
| **Drug(s) Applied:** | Zolgensma® |
| **Original Policy Date:** | 03/06/2020 |
| **Last Review Date:** | 12/07/2020 |
| **Line of Business Policy Applies to:** | All lines of business |

## Background

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

## Dosing Information

| Drug Name | Indication | Dosing Regimen | Maximum Dose |
|---|---|---|---|
| onasemnogene abeparvovec (Zolgensma®) | SMA | Administer Zolgensma as a single-dose IV infusion over 60 minutes at the dose of 1.1 x $10^{14}$ vg/kg.<br><br>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. | Once |

## Dosage Forms

- 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 x $10^{13}$ vg/mL.

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

## Clinical Policy

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

**I. 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 a neurologist;
5. Age less than 2 years of age;
6. 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;
7. Documentation of both of the following (a and b):
   a. Baseline laboratory tests demonstrating Anti-AAV9 antibody titers ≤ 1:50 as determined by ELISA binding immunoassay;
   b. Baseline liver function test, platelet counts, and troponin-I;
   c. Member does not have advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence, tracheostomy, non-invasive ventilation beyond the use for sleep);
8. Member has not been previously treated with Zolgensma®;
9. Zolgensma® is not prescribed concurrently with Spinraza®;
10. 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 that Spinraza will be discontinued upon the initiation of Zolgensma;
11. Member does not have an active viral infection (see Appendix D);
12. Total dose does not exceed 1.1 x $10^{14}$ vector genomes (vg) per kilogram (kg).

**Approval Duration**
**Commercial:** 28 days (one time infusion per lifetime)
**Medicaid:** 28 days (one time infusion per lifetime)

**II. Continued Therapy Approval**

**A. Spinal Muscular Atrophy**

1. Re-authorization is not permitted.

**Approval Duration**

**Commercial:** Not applicable
**Medicaid:** Not applicable

## III. Appendices

**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):
  - acute serious liver injury and elevated aminotransferases

**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.
- 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.

**References**

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| Review/Revision History | Review/Revision Date | P&T Approval Date |
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| Policy established. | 01/2020 | 03/06/2020 |
| Policy was reviewed:<br>1. Clinical Policy title updated<br>2. Line of policy business applies to was updated to All lines of business<br>3. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..."<br>4. Reference were reviewed and updated.<br>5. Clarified I.A.10.b. | 12/03/2020 | 12/07/2020 |