Medical Policy
Zolgensma (onasemnogene abeparvovec-xioi) for Spinal Muscular Atrophy (SMA)

Table of Contents
• Policy: Commercial
• Policy: Medicare
• Authorization Information
• Coding Information
• Description
• Policy History
• Information Pertaining to All Policies
• References

Policy Number: 008
BCBSA Reference Number: 5.01.28
NCD/LCD: N/A

Related Policies
• Spinal Muscular Atrophy (SMA) Medications, #044
• Prior Authorization Request Form for Zolgensma (onasemnogene abeparvovec-xioi) for Spinal Muscular Atrophy (SMA), #085

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Zolgensma™ (onasemnogene abeparvovec-xioi) may be considered MEDICALLY NECESSARY if all of the following conditions are met:

1. Diagnosis of spinal muscular atrophy confirmed by genetic testing demonstrating bi-allelic mutations in the survival motor neuron 1 (SMN1) gene as stated below:
   a. Deletion of both copies of the SMN1 gene; OR
   b. Compound heterozygous mutations of the SMN1 gene (defined below):
      i. Pathogenic variant(s) in both copies of the SMN1 gene; OR
      ii. Pathogenic variant in 1 copy and deletion of the second copy of the SMN1 gene; AND
2. Documentation of a genetic test confirms no more than 4 copies of the SMN2 gene; AND
3. The individual is less than 2 years of age at the time of infusion of onasemnogene abeparvovec-xioi; AND
4. Documentation of baseline laboratory assessments such as AST, ALT, total bilirubin, and prothrombin time; AND
5. The individual does not have advanced spinal muscular atrophy (e.g., complete paralysis of limbs, permanent ventilator dependence); AND
6. Baseline anti-adeno-associated virus serotype 9 (AAV9) antibody titers ≤ 1:50; AND
7. Prescribed by a neurologist with expertise in treating spinal muscular atrophy.
If the member is currently receiving Nusinersen, he/she will be eligible to switch to Zolgensma, but Zolgensma and Nusinersen may not be used concomitantly.

Presymptomatic members identified through the newborn screening process are eligible for treatment pending satisfaction of other clinical requirements.

Repeat treatment or ante-partum use of Zolgensma is considered INVESTIGATIONAL.

Zolgensma is considered INVESTIGATIONAL for all other indications.

Concurrent use of Zolgensma and Nusinersen is considered INVESTIGATIONAL.

Additional Information
The recommended dosage of Zolgensma is $1.1 \times 10^{14}$ vector genomes (vg) per kg of body weight. It should be administered as an intravenous infusion over 60 minutes. Systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg should be administered according to the FDA approved prescribing label.

FDA has issued a black-box warning for Zolgensma due to the risk of acute serious liver injury and elevated aminotransferases. Patients with pre-existing liver impairment may be at higher risk.

The FDA label states that “The safety and efficacy of Zolgensma in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated.” Baseline anti-AAV9 antibody testing is performed prior to infusion using. Retesting may be performed if anti-AAV9 antibody titers are reported as >1:50.

Liver function (clinical exam, AST, ALT, total bilirubin, prothrombin time), platelet counts, and troponin-I levels should be monitored as per the prescribing label.

Where feasible, patient’s vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following Zolgensma infusion.

Use of Zolgensma in premature neonates before reaching full term gestational age may not be recommended because concomitant treatment with corticosteroids may adversely affect neurological development.

Efficacy of Zolgensma in patients with c.859G>C variant in SMN2 gene has not been evaluated.

Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient
- For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Prior authorization is required.*</th>
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<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>Prior authorization is required.*</td>
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<tr>
<td>Medicare HMO Blue℠</td>
<td>Prior authorization is required.*</td>
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<tr>
<td>Medicare PPO Blue℠</td>
<td>Prior authorization is required.*</td>
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Prior Authorization Request Form: Zolgensma™ (onasemnogene abeparvovec-xioi) for Spinal Muscular Atrophy (SMA)

*This form must be completed and faxed to: Medical and Surgical: 1-888-282-0780; Medicare Advantage: 1-800-447-2994.
CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitutes or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

<table>
<thead>
<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>C9399</td>
<td>Unclassified drugs or biologicals</td>
</tr>
<tr>
<td>J3399</td>
<td>Injection, Onasemnogene abeparvovec-xioi, per treatment, up to 5x10^15 vector genomes</td>
</tr>
<tr>
<td>J3490</td>
<td>Unclassified drugs</td>
</tr>
<tr>
<td>J3590</td>
<td>Unclassified biologics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10 Procedure Codes</th>
</tr>
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<tbody>
<tr>
<td>ICD-10-PCS codes:</td>
</tr>
<tr>
<td>XW033F3</td>
</tr>
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</table>

The following ICD Diagnosis Code is considered medically necessary when submitted with the codes above if medical necessity criteria are met:

<table>
<thead>
<tr>
<th>ICD-10 Diagnosis Codes</th>
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<tbody>
<tr>
<td>ICD-10-CM diagnosis codes:</td>
</tr>
<tr>
<td>G12.0</td>
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Description
Spinal Muscular Atrophy
SMA is a rare autosomal recessive genetic disorder caused by homozygous deletions or variants in the SMN1 gene located on chromosome 5. This gene produces the “survival of motor neuron” protein (SMN1), which is essential for motor neuron functioning. In 95% of cases of SMA, there is a homozygous deletion of exon 7 in the SMN1 gene. The remaining 5% of cases are compound heterozygotes for SMN1 exon 7 deletions and small intragenic variants. Due to absent or low levels of the SMN1 protein, motor neurons in the spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk affecting the ability to crawl, walk, sit up, and control head. In more severe cases, feeding, swallowing, and breathing are affected as well. The exact role of the SMN protein in motor
neurons has not been completely elucidated, and levels of the SMN protein required for optimal functioning are unknown.²

There is wide phenotypic heterogeneity in SMA, as summarized in Table 1. This is due to the presence of SMN2, a modifying/backup gene, also located on chromosome 5, which is 99% identical to SMN1. However, 70% to 90% of the SMN2 compensatory protein produced by this gene is defective and unstable due to the lack of exon 7.³ The number of copies of the SMN2 gene varies widely (range, 0-6), resulting in a less severe form of SMA among those with more copies of the SMN2 gene and vice-versa.² The relation between the SMN2 copy number and SMA phenotype is summarized in Table 2. These data were generated from DNA samples of 375 patients with SMA who previously had been classified as follows: 188 with SMA type I, 110 with SMA type II, and 77 with SMA type III.³

Table 1. Characteristics and Subtypes of SMA

<table>
<thead>
<tr>
<th>Type of SMA</th>
<th>Age at Symptoms Onset</th>
<th>Life Span</th>
<th>Highest Motor Milestone Achieved</th>
<th>SMN2 Copy Number³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 0 (antenatal-onset SMA)</td>
<td>Prenatal</td>
<td>&lt;6 mo</td>
<td>Little ability to move and may be unable to breathe and swallow independently</td>
<td>1</td>
</tr>
<tr>
<td>Type I (infantile SMA or Werndig-Hoffman disease)</td>
<td>0-6 mo</td>
<td>&lt;2 y without respiratory support</td>
<td>Never rolls or sits unsupported</td>
<td>2</td>
</tr>
<tr>
<td>Type II (intermediate SMA or Dubowitz disease)</td>
<td>&lt;18 mo</td>
<td>&gt;2 y; &gt;70% alive at 25 y of age</td>
<td>Sits independently once properly positioned; sometimes stands but never able to walk</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Type III (Kugelberg-Welander disease)</td>
<td>&gt;18 mo to 3 y</td>
<td>Similar to that of the general population</td>
<td>Sits, stands, and walks independently until puberty; many no longer walk after puberty. Never runs or jumps well</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Subtype IIIa</td>
<td>&gt;18 mo to 3 y</td>
<td>Similar to that of the general population</td>
<td>Sits, stands, and walks independently until puberty; many no longer walk after puberty. Never runs or jumps well</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Subtype IIIb</td>
<td>&gt;3 y</td>
<td>Similar to that of the general population</td>
<td>Sits, stands, and walks independently until puberty; many no longer walk after puberty. Walks, runs, jumps, and can participate in sports</td>
<td>4</td>
</tr>
<tr>
<td>Type IV (adult-onset SMA)</td>
<td>&gt;21 y</td>
<td>Similar to that of the general population</td>
<td>Similar to that of the general population</td>
<td>4-8</td>
</tr>
</tbody>
</table>


SMN: spinal muscular atrophy

³ Quantitative analysis of SMN2 copies in 375 patients showed that 80% of SMA type I carry 1 or 2 SMN2 copies, 82% with SMA type II carry 3 SMN2 copies, and 96% with SMA type III carry 3 or
Among 113 patients with SMA type I, 9 with 1 SMN2 copy lived <11 months, 88 of 94 with 2 SMN2 copies lived <21 months, and 8 of 10 with 3 SMN2 copies lived 33 to 66 months.\textsuperscript{11}

### Table 2. Relation Between \textit{SMN2} Copy Numbers and SMA Phenotype

<table>
<thead>
<tr>
<th>Type of SMA</th>
<th>Percent With 1 SMN2 Copy</th>
<th>Percent With 2 SMN2 Copies</th>
<th>Percent With 3 SMN2 Copies</th>
<th>Percent With 4 SMN2 Copies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>6.9</td>
<td>73.4</td>
<td>19.7</td>
<td>0</td>
</tr>
<tr>
<td>Type II</td>
<td>0</td>
<td>10.9</td>
<td>81.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Type III</td>
<td>0</td>
<td>3.9</td>
<td>50.6</td>
<td>45.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probability\textsuperscript{a} of SMA Type I</th>
<th>Probability\textsuperscript{a} of SMA Type II</th>
<th>Probability\textsuperscript{a} of SMA Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SMN2 copy</td>
<td>99.9</td>
<td>0</td>
</tr>
<tr>
<td>2 SMN2 copies</td>
<td>97.3</td>
<td>2.7</td>
</tr>
<tr>
<td>3 SMN2 copies</td>
<td>7.2</td>
<td>82.8</td>
</tr>
<tr>
<td>4 SMN2 copies</td>
<td>1.6</td>
<td>14.8</td>
</tr>
</tbody>
</table>

Adapted from Feldkotter et al (2002).\textsuperscript{5}

\textsuperscript{a} Probability that an unaffected child who has been tested after birth and has been found to carry a homozygous \textit{SMN1} deletion will develop SMA type.

### Diagnosis

SMA can be diagnosed using multiple molecular genetic testing techniques such as multiplex ligation-dependent probe amplification or quantitative polymerase chain reaction or a comprehensive next-generation sequencing-based approach. Individuals are classified as having SMA if they have a homozygous deletion of the \textit{SMN1} gene or a homozygous absence of the \textit{SMN1} gene due to gene conversion (ie, \textit{SMN1} gene conversion to \textit{SMN2} gene) or a compound heterozygote variant in the \textit{SMN1} gene. Individuals are defined as carriers if they have one copy of the \textit{SMN1} gene on one chromosome and no copies on the other or two copies of the \textit{SMN1} gene on one chromosome and no copies on the other. Assessing \textit{SMN2} copy numbers as part of a diagnostic workup is important because it can provide critical information on disease progression and assist in possible clinical trial enrollment or treatment.

Because SMA symptom onset may occur shortly after birth to months to years later, estimating the incidence and prevalence of SMA subtypes is difficult. The incidence, as reported in the literature, is more precisely a birth prevalence rate, which is estimated between 9.1 and 10 per 100000 live births,\textsuperscript{12} which translates to 500 new SMA cases annually.

### Treatment

Medical management of SMA patients includes respiratory, nutritional, and musculoskeletal supportive care. Respiratory management includes airway clearance, antibiotic treatment of infections, noninvasive and invasive ventilation. Nutritional management includes changing food consistency, gastrostomy tube feeding, and dietician assessment. Musculoskeletal supportive care includes a variety of intervention such as equipment for mobility, teaching self-care and function, physiotherapy, spinal surgery, posture and pain management, regular exercise, and scoliosis surgery. The type and extent of supportive care can affect survival in infant-onset disease (eg, gastrostomy feeding and noninvasive/invasive ventilation).

Zolgensma™ (onasemnogene abeparvovec-xioi), a one-time gene replacement therapy is intended as an intravenous infusion for patients with SMA type I and an intrathecal infusion for SMA type II. There are four major components of this technology—the vector, the \textit{SMN} transgene, the self-complementary DNA technology, and the promoter.\textsuperscript{12} A brief description of each component is provided below.

- **Vector**: Nonreplicating adeno-associated virus serotype 9 that easily crosses the blood-brain barrier.
• **Transgene**: Nonintegrating copy of a stable and fully functioning human *SMN* gene that is introduced into the motor neuron cells. The gene is designed to stay in the nucleus and does not alter the patient’s genome.

• **Self-complementary adeno-associated virus Inverted Terminal Repeats**: Use of self-complementary adeno-associated virus inverted terminal repeats obviates the dependence of the transgene on the patient’s motor neuron-mediated synthesis of a complementary DNA strand to form the double-stranded DNA. Instead, the transgene is self-complementary, enabling rapid onset of effect.

• **Promoter**: The technology uses a chicken beta-actin hybrid promoter, which functions as a continuous promoter allowing for sustained expression of the SMN protein.

Because motor neurons are nondividing cells, it is has been suggested that once the *SMN* gene is incorporated in the cells, it would be retained over time and potentially allow for long-term, sustained SMN protein expression with a one-time dose, and provide a durable therapeutic effect based on studies in animal models.

**Summary**

Spinal muscular atrophy (SMA) is an inherited disorder caused by homozygous deletions or variants in the *SMN1* gene. As a consequence of absent or low levels of SMN1 protein, the motor neurons in spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk. Zolgensma™ (onasemnogene abeparvovec-xioi) is intended as a one-time gene replacement therapy designed to deliver a functional copy of the *SMN1* gene to motor neuron cells of patients with SMA. Because motor neurons are nondividing cells, it is postulated that once the *SMN1* gene is incorporated in the cells, it would be retained over time and potentially allow for long-term, sustained SMN protein expression.

**Onasemnogene Abeparvovec-Xioi**

**Infantile-Onset or SMA Type I**

For individuals who have SMA type I (infantile-onset) who receive Zolgensma™ (onasemnogene abeparvovec-xioi), the evidence includes a prospective cohort of 15 patients followed for 2 years. Relevant outcomes are overall survival, change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. In this single phase 1 study of symptomatic infants with 2 copies of *SMN2* gene, 12 of 15 infants received the proposed therapeutic dose while 3 received the minimally effective dose. At the end of the 2-year follow-up, all 15 infants survived and none of the 12 patients who received the proposed therapeutic dose required permanent ventilation. All 12 patients also achieved at least 1 motor milestone, with 92% of those achieving scores greater than 40 on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (a score >40 is a favorable outcome). The FDA approval was based on a pooled analysis of 21 patients from the pivotal phase I and ongoing confirmatory phase III STRIVE-US trial. The observed treatment effect on survival, event-free survival and achievement of motor functions is beyond what is typical based on the known natural history of patients with SMA type I with two copies of *SMN2*. The available published data support a clinically meaningful durable treatment effect through 2 years. However, there is limited data to assess the long-term durability of treatment effect as well as safety related to adverse events that are rare or have delayed onset. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Presymptomatic Patients with a Diagnosis of SMA and Less Than 3 Copies of SMN2**

For individuals who are presymptomatic with a genetic diagnosis of SMA and less than 3 copies of SMN2 who receive Zolgensma™ (onasemnogene abeparvovec-xioi), the evidence includes a prospective cohort with a planned enrollment of 44 patients and a planned follow-up of 18 to 24 months. Relevant outcomes are overall survival, change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. The single prospective cohort study (SPRINT) is currently ongoing. As of March 2019, 18 patients have been treated. The median follow-up after treatment was 2.9 months (range 0.4 to 8.7). All 18 children were alive and “event free.” Among 8 patients with two copies of SMN2, all reportedly achieved age-appropriate motor milestones including 4 who could sit without support and 1 who could
stand with assistance. Data was much more limited for patients with 3 copies of SMN2. However, early increases in mean Bayley-III Gross Motor score were observed. The evidence for presymptomatic SMA patients is currently evolving.

**SMA Type II**

For individuals with SMA type II who receive intrathecal Zolgensma™ (onasemnogene abeparvovec-xioi), the evidence includes a single prospective cohort study with a planned enrollment of 27 patients who are up to 60 months old. Relevant outcomes are overall survival, change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. The single prospective cohort study (STRONG) evaluating use of intrathecal Zolgensma™ (onasemnogene abeparvovec-xioi) administration in patients with age of symptom onset up to 60 months is currently ongoing. The data is premature but suggests some benefit as a number of patients achieved new motor milestones. The evidence is insufficient to determine the effects of technology on health outcomes.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>8/2023</td>
<td>Policy revised:</td>
</tr>
<tr>
<td></td>
<td>• Updated number of SMN2 copies requirement from no more than 3 to 4. Effective 8/9/2023.</td>
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<tr>
<td></td>
<td>• Updated to match BCBSA updates - removed the weight requirement of ≤13.5kg at time of infusion; added new criteria requirement for baseline liver function. Policy updated for with literature review. Policy statement updated. References updated. Effective 8/9/2023.</td>
</tr>
<tr>
<td>7/2020</td>
<td>Clarified coding information</td>
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</table>

**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**


Based on expert opinion.