# Medical Policy

BlueCross BlueShield Kansas
An Independent licensee of the Blue Cross Blue Shield Association

# Title: Zolgensma Medical Drug Criteria

| **Professional / Institutional** |
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| Original Effective Date: August 25, 2022 |
| Latest Review Date: September 21, 2023 |
| Current Effective Date: September 21, 2023 |

**State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.**

**The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.**

**The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.**

**If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.**

FDA APPROVED INDICATIONS AND DOSAGE

| Agent(s) | FDA Indication(s) | Notes | Ref# |
|---|---|---|---|
| Zolgensma® (onasemnogene abeparvovec-xioi)<br><br>Intravenous infusion | Treatment of pediatric patients less than two years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene<br><br>Limitations of use:<br>• The safety and effectiveness of repeat administration of Zolgensma have not been evaluated<br>• The use of Zolgensma in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated | | 1 |

*See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm*

## CLINICAL RATIONALE

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder, caused by bi-allelic loss or dysfunction of the survival motor neuron (SMN) gene. The two versions of SMN, SMN1 and SMN2, differ by only five nucleotides. SMN1 produces a full-length transcript that encodes functional SMN protein. About 94% of SMA patients have a homozygous deletion of SMN1 exon 7. SMN1 can be absent because of deletion or SMN1-to-SMN2 conversion. The SMN1 and SMN2 genes are all located at 5q13.2, an unstable chromosomal region that is prone to deletion, duplication, and gene conversion. A single nucleotide transition in SMN2 exon7 relative to SMN1 causes most of the SMN2 pre-mRNA to lack exon 7 and encode nonfunctional SMNΔ7 protein. However, about 10% of SMN2 pre-mRNA is normal and can be translated into full-length SMN protein.(9) Insufficient levels of the survival motor neuron protein result in a loss of motor neurons of the brainstem and spinal cord, progressive muscular atrophy, and weakness. SMA has an incidence of approximately 1 in 10,000 live births and a carrier frequency of approximately 1 in 54. SMA is classified into four subtypes (1-4) based on age of onset of symptoms and motor milestone
achievement. This variability in the clinical phenotype is largely a result of the number of copies of the survival motor neuron gene 2 (SMN2), which produces a small, insufficient amount of SMN protein. The SMA type 1 (SMA1) phenotype is the most severe, and accounts for 60% of SMA patients.(2) The presence of two copies of SMN2 is associated with SMA1. Infants with SMN1 bi-allelic deletions and two copies of SMN2 have a 97% risk of SMA1.(3)

Clinical Classification of SMA(4)

| SMA Type | Age of Onset | Highest Achieved Motor Function | Natural Age of Death | Typical Number of SMN2 Copies(5) |
|---|---|---|---|---|
| 0 | Prenatal /fetal | None | <6 months | 1 |
| 1 | <6 months | Sit with support only | <2 years | 1-3 |
| 2 | 6-18 months | Sit independently | >2 years | 2-3 |
| 3 | >18 months | Walk independently | Adulthood | 3-4 |
| 4 | Adult (20s-30s) | Walk through adulthood | Adulthood | ≥4 |

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| | The onset of symptoms for SMA1 occurs shortly after birth and prior to six months of age with a clinical hallmark of the inability to achieve independent sitting.(2) A historical cohort showed that the median age at symptom onset among infants with the disease was 1.2 months (range, 0 to 4 months).(3) Infants with SMA1 rapidly lose motor function and ultimately succumb to respiratory complications often within the first year of life. Studies of SMA1 infants with two SMN2 copies offered standard of care showed a median age of death or permanent ventilation (greater than or equal to 16h/day for at least 14 consecutive days) that ranged from 8 to 10.5 months.(2) Patients with SMA1 do not achieve major milestones in function and have a decline in function, as measured on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scale, which ranges from 0 to 64, with higher scores indicating better motor function. In a historical analysis of 34 patients with SMA1, all but one of the patients did not reach a score of at least 40 after 6 months of age. In another cohort, CHOP-INTEND scores decreased by a mean of 10.7 points from 6 months to 12 months of age.(3)<br><br>Molecular genetic testing is the standard tool for diagnosis of SMA. Genetic testing for homozygous deletion will confirm the disease in 95% of patient. Essentially all other patients with SMN-related SMA will be compound heterozygotes with a single SMN1 deletion and a mutation in the other SMN1 copy.(8)<br><br>Zolgensma is a gene therapy that is given as a one-time IV administration that delivers a copy of SMN in a self-complementary adeno-associated viral serotype 9 (scAAV9). This has induced SMN expression in motor neurons and peripheral tissues. Its efficacy was evaluated in an ongoing open-label, single-arm clinical trial and a completed open-label, single arm, ascending-dose clinical trial. Patients studied experienced onset of clinical symptoms consistent with SMA before 6 months of age. All had genetically confirmed bi-allelic SMN1 gene deletions, 2 copies of the SMN2 gene, and absence of the c.859G greate than C modification in exon 7 of SMN2 gene.(3) A study of the c.859G greater than C modification variant led researchers to conclude that this variant is a milder SMA allele, which is present in a minority of patients with chronic SMA, but not in any with type 1 disease.(6) All patients had baseline anti-AAV9 antibody titers of less than or equal to 1:50 as measured by ELISA(7). Efficacy was established based on survival and achievement of developmental motor milestones. Survival was defined as time from birth to either death or permanent ventilation. Efficacy was also supported by assessments of ventilator use, nutritional support and CHOP-INTEND scores. In the ongoing trial, 21 patients were enrolled, none of which required non-invasive ventilator support and all could exclusively feed orally. At the time of data cutoff, 19 patients were alive without permanent ventilation and continuing in the trial. One patient died at age 7.8 months due to disease progression, and one patient withdrew at age 11.9 months. Thirteen of the nineteen patients reached 14 months of age without permanent ventilation. Ten of 21 patients achieved the ability to sit without support for greater than or equal<br>to 30 seconds between 9.2 and 16.9 months of age (mean 12.1 months). Based on the natural history of the disease, patients who met the study entry criteria would not attain the ability to sit without support, and only approximately 25% of these patients would be expected to survive without permanent ventilation beyond 14 months of age.(1) |

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder, caused by bi-allelic loss or dysfunction of the survival motor neuron (SMN) gene. The two versions of SMN, SMN1 and SMN2, differ by only five nucleotides. SMN1 produces a full-length transcript that encodes functional SMN protein. About 94% of SMA patients have a homozygous deletion of SMN1 exon 7. SMN1 can be absent because of deletion or SMN1-to-SMN2 conversion. The SMN1 and SMN2 genes are all located at 5q13.2, an unstable chromosomal region that is prone to deletion, duplication, and gene conversion. A single nucleotide transition in SMN2 exon7 relative to SMN1 causes most of the SMN2 pre-mRNA to lack exon 7 and encode nonfunctional SMNΔ7 protein. However, about 10% of SMN2 pre-mRNA is normal and can be translated into full-length SMN protein.(9) Insufficient levels of the survival motor neuron protein result in a loss of motor neurons of the brainstem and spinal cord, progressive muscular atrophy, and weakness. SMA has an incidence of approximately 1 in 10,000 live births and a carrier frequency of approximately 1 in 54. SMA is classified into four subtypes (1-4) based on age of onset of symptoms and motor milestone
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|---|---|
| Efficacy | The complete clinical trial enrolled 15 patients with infantile-onset SMA, with genetically confirmed diagnosis of SMA1, homozygous SMN1 exon 7 deletions, and two copies of SMN2, with absence of the c.859G greater than C modification. Of the 16 patients screened, 1 was excluded because of persistently elevated anti-AAV9 titers greater than 1:50. Three patients were assigned to the low-dose ($6.7x10^{13}$ VG/kg) cohort, the remaining 12 received high dose ($2.0x10^{14}$ VG/kg). Average age for cohort 1 at time of treatment was 6.3 months (range 5.9 to 7.2), while average age in cohort 2 was 3.4 months (range 0.9 to 7.9). Patient 1 in cohort 1 resulted with serum aminotransferase elevations, which led to a protocol amendment. Patients 2 through 15 received oral prednisolone 1mg/kg daily for 30 days, starting 24 hours before the administration of Zolgensma. The primary outcome was the determination of safety based on any treatment-related adverse events of grade 3 or higher. The secondary outcome was the time until death or the need for permanent ventilatory assistance.<br>Exploratory outcomes included motor-milestone achievements and CHOP-INTEND scores. At the end of the study, all patients had reached an age of at least 20 months and did not require permanent mechanical ventilation. At 29 months of age, one patient required permanent ventilation because of hypersalivation. All patients had increased scores from baseline on the CHOP-INTEND scale and maintained these changes during the study. Eleven of twelve patients in cohort 2 were able to sit unassisted for at least 5 seconds, ten for at least 10 seconds, and 9 for at least 30 seconds. Other motor milestones were also positive, and eleven of twelve attained the ability to speak. No patients in historical cohorts had achieved any of these motor milestones and rarely achieved the ability to speak.(3)<br><br>In Zolgensma clinical trials, patients were required to have baseline anti-AAV9 antibody titers of less than or equal to 1:50, measured using an enzyme-linked immunosorbent assay (ELISA). The safety and efficacy of Zolgensma in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated. Starting one day prior to Zolgensma infusion, patients should receive systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg of body weight per day for a total of 30 days. At the end of systemic corticosteroid treatment, check liver function be clinical examination and by laboratory testing.(1) |
| Safety | Zolgensma has no contraindications.(1)<br><br>Zolgensma has the following boxed<br><br>warnings:(1)<br><br>• Acute serious liver injury and elevated aminotransferases can occur with Zolgensma.<br>• Patients with pre-existing liver impairment may be at higher risk.<br>• Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Administer systemic corticosteroid to all patients before and after Zolgensma infusion. Continue to monitor liver function for at least 3 months after infusion. |

## REFERENCES


| Number | Reference |
|---|---|
| 1 | Zolgensma prescribing information. AveXis, Inc. October 2021. |
| 2 | Al-Zaidy S, Pickard AS, Kotha K, e. al.Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy.Pediatric Pulmonology 2019;54:179-185. |
| 3 | Mendell JR, Al-Zaidy S, Shell R, et al.Single-Dose Gene Replacement Therapy for Spinal Muscular Atrophy.N Engl J Med 2017;377:1713-22 |
| 4 | Verhaart IEC, RobertsonA, Wilson IJ, et al.Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy – a literature review. Orphanet J Rare Dis. 2017;12(1):124 |
| 5 | Calucho M, Bernal S, Alias L, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord. 2018;28(3):208-215. |
| 6 | Bernal S, Alias L, Barcelo MJ, et al.The c.859G>C variant in the SMN2 gene is associated with both type II and III SMA and originates from a common ancestor.Journal of Medical Genetics, BMJ Publishing Group, 2010, 47 (9) pp. 640. |
| 7 | Mendell, JR, Kaspar BK, Burghes A. Phase I Gene transfer clinical trial for spinal muscular atrophy type 1 delivering the survival motor neuron gene by self-complimentary AAV9. Phase I Clinical Study Protocol, Version 1.0, October 5, 2012. |
| 8 | Arnold WA, Kassar D, Kissel JT. Spinal Muscular Atrophy: Diagnosis and Management in a New Therapeutic Era. Muscle Nerve 2015 Feb; 51(2): 157-167. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4293319/ |
| 9 | Fang P, Li L, Zeng J, et al. Molecular Characterization and Copy Number of SMN1, SMN2 and NAIP in Chinese Patients with Spinal Muscular Atrophy and Unrelated Healthy Controls. B<C Musculoskelet Disord. 2015; 16(1):11. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4328246/ |


## POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

| Final Module | Wildcard | HCPC Codes | Target Brand Agent Name(s) | Target Generic Agent Name(s) | Strength | Targeted MSC | Targeted NDCs When Exclusions Exist | Final Age Limit | Preferred Status | Effective Date |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |
| | 747040501064 | J3399 | Zolgensma 10.1-10.5 kg ; Zolgensma 10.6-11.0 kg ; Zolgensma 11.1-11.5 kg ; Zolgensma 11.6-12.0 kg ; Zolgensma 12.1-12.5 kg ; Zolgensma 12.6-13.0 kg ; Zolgensma 13.1-13.5 kg ; Zolgensma 13.6-14.0 kg ; Zolgensma 14.1-14.5 kg ; Zolgensma 14.6-15.0 kg ; Zolgensma 15.1-15.5 kg ; Zolgensma 15.6-16.0 kg ; Zolgensma 16.1-16.5 kg ; | onasemnogene abeparvovec-xioi | 10x8.3 ML ; 11x8.3 ML ; 12x8.3 ML ; 13x8.3 ML ; 14x8.3 ML ; 1x5.5ML & 10x8.3ML ; 1x5.5ML & 11x8.3ML ; 1x5.5ML & 12x8.3ML ; 1x5.5ML & 13x8.3ML ; 1x5.5ML & 2x8.3ML ; 1x5.5ML & 3x8.3ML ; 1x5.5ML & 4x8.3ML ; 1x5.5ML & 5x8.3ML ; 1x5.5ML & 6x8.3ML ; 1x5.5ML & 7x8.3ML ; 1x5.5ML & | M ; N ; O ; Y | | | | 04-14-2023 |

| Final Module | Wildcard | HCPC Codes | Target Brand Agent Name(s) | Target Generic Agent Name(s) | Strength | Targeted MSC | Targeted NDCs When Exclusions Exist | Final Age Limit | Preferred Status | Effective Date |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Zolgensma 16.6-17.0 kg ; Zolgensma 17.1-17.5 kg ; Zolgensma 17.6-18.0 kg ; Zolgensma 18.1-18.5 kg ; Zolgensma 18.6-19.0 kg ; Zolgensma 19.1-19.5 kg ; Zolgensma 19.6-20.0 kg ; Zolgensma 2.6-3.0 kg ; Zolgensma 20.1-20.5 kg ; Zolgensma 20.6-21.0 kg ; Zolgensma 3.1-3.5 kg ; Zolgensma 3.6-4.0 kg ; Zolgensma 4.1-4.5 kg ; Zolgensma 4.6-5.0 kg ; Zolgensma 5.1-5.5 kg ; Zolgensma 5.6-6.0 kg ; Zolgensma 6.1-6.5 kg ; Zolgensma 6.6-7.0 kg ; Zolgensma 7.1-7.5 kg ; Zolgensma 7.6-8.0 kg ; Zolgensma 8.1-8.5 kg ; Zolgensma 8.6- | | 8x8.3ML ; 1x5.5ML & 9x8.3ML ; 2x5.5ML & 10x8.3ML ; 2x5.5ML & 11x8.3ML ; 2x5.5ML & 12x8.3ML ; 2x5.5ML & 1x8.3ML ; 2x5.5ML & 2x8.3ML ; 2x5.5ML & 3x8.3ML ; 2x5.5ML & 4x8.3ML ; 2x5.5ML & 5x8.3ML ; 2x5.5ML & 6x8.3ML ; 2x5.5ML & 7x8.3ML ; 2x5.5ML & 8x8.3ML ; 2x5.5ML & 9x8.3ML ; 2x8.3 ML ; 3x8.3 ML ; 4x8.3 ML ; 5x8.3 ML ; 6x8.3 ML ; 7x8.3 ML ; 8x8.3 ML ; 9x8.3 ML | | | | | |
| | | | 9.0 kg ; Zolgensma 9.1-9.5 kg ; Zolgensma 9.6-10.0 kg | | | | | | | |

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## CLIENT SUMMARY – PRIOR AUTHORIZATION

| Target Brand Agent(s) | Target Generic Agent(s) | Strength | Client Formulary |
|---|---|---|---|
| | | | |
| Zolgensma 10.1-10.5 kg ; Zolgensma 10.6-11.0 kg ; Zolgensma 11.1-11.5 kg ; Zolgensma 11.6-12.0 kg ; Zolgensma 12.1-12.5 kg ; Zolgensma 12.6-13.0 kg ; Zolgensma 13.1-13.5 kg ; Zolgensma 13.6-14.0 kg ; Zolgensma 14.1-14.5 kg ; Zolgensma 14.6-15.0 kg ; Zolgensma 15.1-15.5 kg ; Zolgensma 15.6-16.0 kg ; Zolgensma 16.1-16.5 kg ; Zolgensma 16.6-17.0 kg ; Zolgensma 17.1-17.5 kg ; Zolgensma 17.6-18.0 kg ; Zolgensma 18.1-18.5 kg ; Zolgensma 18.6-19.0 kg ; Zolgensma 19.1-19.5 kg ; Zolgensma 19.6-20.0 kg ; Zolgensma 2.6-3.0 kg ; Zolgensma 20.1-20.5 kg ; Zolgensma 20.6-21.0 kg ; Zolgensma 3.1-3.5 kg ; Zolgensma 3.6-4.0 kg ; Zolgensma 4.1-4.5 kg ; Zolgensma 4.6-5.0 kg ; Zolgensma 5.1-5.5 kg ; Zolgensma 5.6-6.0 kg ; Zolgensma 6.1-6.5 kg ; Zolgensma 6.6-7.0 kg ; Zolgensma 7.1-7.5 kg ; Zolgensma 7.6-8.0 kg ; Zolgensma 8.1-8.5 kg ; Zolgensma 8.6-9.0 kg ; Zolgensma 9.1-9.5 kg ; Zolgensma 9.6-10.0 kg | onasemnogene abeparvovec-xioi | 10x8.3 ML ; 11x8.3 ML ; 12x8.3 ML ; 13x8.3 ML ; 14x8.3 ML ; 1x5.5ML & 10x8.3ML ; 1x5.5ML & 11x8.3ML ; 1x5.5ML & 12x8.3ML ; 1x5.5ML & 13x8.3ML ; 1x5.5ML & 2x8.3ML ; 1x5.5ML & 3x8.3ML ; 1x5.5ML & 4x8.3ML ; 1x5.5ML & 5x8.3ML ; 1x5.5ML & 6x8.3ML ; 1x5.5ML & 7x8.3ML ; 1x5.5ML & 8x8.3ML ; 1x5.5ML & 9x8.3ML ; 2x5.5ML & 10x8.3ML ; 2x5.5ML & 11x8.3ML ; 2x5.5ML & 12x8.3ML ; 2x5.5ML & 1x8.3ML ; 2x5.5ML & 2x8.3ML ; 2x5.5ML & 3x8.3ML ; 2x5.5ML & 4x8.3ML ; 2x5.5ML & 5x8.3ML ; 2x5.5ML & 6x8.3ML ; 2x5.5ML & 7x8.3ML ; 2x5.5ML & 8x8.3ML ; 2x5.5ML & 9x8.3ML ; 2x8.3 ML ; 3x8.3 ML ; 4x8.3 ML ; 5x8.3 ML ; 6x8.3 ML ; 7x8.3 ML ; 8x8.3 ML ; 9x8.3 ML | |

**Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

## PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

| Module | Clinical Criteria for Approval |
|---|---|
| | **Evaluation**<br><br>**Target Agent(s)** will be approved when ALL of the following are met:<br><br>1. The patient has a diagnosis of spinal muscular atrophy (SMA) **AND**<br>2. Information has been provided that indicates the patient has bi-allelic mutations in the survival motor neuron 1 (SMN1) gene as confirmed by genetic testing (medical records required) **AND**<br>3. The patient has 4 or fewer copies of the SMN2 gene (medical records required) **AND**<br>4. The patient is less than 2 years of age **AND**<br>5. The patient has baseline anti-AAV9 antibody titers of less than or equal to 1:50 **AND**<br>6. The patient's pre-treatment liver function has been assessed by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time) **AND**<br>7. The patient will have their liver function monitored for at least 3 months after infusion **AND**<br>8. The patient has been assessed for concurrent infections and no clinical signs or symptoms of infection are evident **AND**<br>9. Pre-infusion blood work, including creatinine, complete blood count (including hemoglobin and platelet count) and troponin-I, has been completed **AND**<br>10. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**<br>11. The patient will receive systemic corticosteroids before and after Zolgensma infusion **AND**<br>12. The patient has not previously been administered Zolgensma **AND**<br>13. The patient does not have advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence [defined as invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in absence of an acute reversible illness, excluding perioperative ventilation]) **AND**<br>14. The patient will NOT receive the requested agent in combination with Spinraza or risdiplam **AND**<br>15. The patient does NOT have any FDA labeled contraindications to the requested agent **AND**<br>16. The requested dose is within FDA labeled dosing for the requested indication<br><br>**Length of Approval:** Once per lifetime |

## PRIOR AUTHORIZATION CLINICAL CRITERIA OPERATIONAL LEVEL OF EVIDENCE REQUIREMENTS

| Module | Ops Set Up | Validation Options | Other Explanation |
|---|---|---|---|
| | Documentation: Requirements as noted within the policy;Validation: Apply Baseline and go to Validation Options | Age Verification | |