Elevance Health FINAL DRAFT – LOGO TO BE INSERTED UPON FINAL PRODUCTION DATE

# Medical Policy

| | | | |
|---|---|---|---|
| **Subject:** | Gene Therapy for Spinal Muscular Atrophy | | |
| **Document#:** | MED.00129 | **Publish Date:** | 09/07/2022~~08/18/2022~~ |
| **Status:** | Revised | **Last Review Date:** | 0~~8~~9/~~11~~xx06/2022 |

## Description/Scope

This document addresses gene therapy for spinal muscular atrophy (SMA), a rare and often fatal genetic disease affecting muscle strength and movement. One gene therapy product, Zolgensma® (onasemnogene abeparvovec-xioi), has been approved by the Food and Drug Administration (FDA).

**Note**: Please refer to clinical pharmacy criteria for information regarding other disease-modifying treatments for SMA; for example: nusinersen (Spinraza) or risdiplam (Evyrsdi).

## Position Statement

**Medically Necessary:**

A one-time infusion of onasemnogene abeparvovec-xioi is considered **medically necessary** in individuals with spinal muscular atrophy (SMA) ~~type 1~~ when **all** of the following criteria are met:

A. Confirmed SMA diagnosis as documented by a bi-allelic SMN1 5q gene variant or deletions and *either* of the following:
   1. No more than 3 copies of SMN2; **or**
   2. Onset of SMA-associated signs and symptoms before 6 months of age; **and**
B. Two years of age or younger at the time of vector infusion; **and**
C. Anti-adeno-associated viral vector, serotype 9 (AAV9) antibody titer less than or equal to 1:50; **and**

D. No use of invasive ventilatory support (tracheotomy with positive pressure) or use of non-invasive ventilator support (BiPAP) for more than 16 hours per day as a result of advanced SMA disease; **and**
E. No serious concomitant illness (for example, severe liver or kidney disease, symptomatic cardiomyopathy, active viral infection).

**Investigational and Not Medically Necessary:**

Onasemnogene abeparvovec-xioi is considered **investigational and not medically necessary** when the criteria above are not met, including for repeat infusions, and for all other indications.

## Rationale

Zolgensma (onasemnogene abeparvovec-xioi) was approved by the FDA on May 24, 2019 for the treatment of individuals less than 2 years of age with SMA who have bi-allelic mutations in the survival motor neuron 1 (SMN1) gene. The product was approved for single intravenous administration only; repeat administration of Zolgensma and its use in individuals with advanced SMA (e.g. need for permanent ventilatory support or complete limb paralysis) have not been evaluated. In clinical trials, the product was known by its former name, AVXS-101.

The FDA approval cites data on the efficacy of Zolgensma in a total of 36 treated individuals. This includes 15 individuals in a completed Phase I open-label, single-arm, ascending-dose clinical trial and 21 individuals in an, at the time, ongoing Phase III trial (using the higher dose in the Phase I trial). Both trials required a confirmed diagnosis of SMA based on gene mutation analysis with bi-allelic SMN1 mutations, either 1 or 2 copies of SMN2, and symptom onset at 6 months of age and earlier, consistent with SMA type 1. Trials also required administration of infusion at 6 months of age or younger (although a single study participant in the Phase I high-dose cohort was older than 6 months of age at study entry [7.9 months]; this individual achieved the fewest major milestones assessed in the study cohort). At the time of treatment, the mean age of individuals was 3.4 months (range 0.9 to 7.9 months) in the high-dose group of the Phase I trial (Mendell, 2017) and 3.9 months (range 0.5 to 5.9 months) in the Phase III trial (Zolgensma product label, 2021).

Trials have excluded individuals with AAAV9 antibody titers > 1:50, serious concomitant illness, and dependence on ventilatory support (tracheotomy with positive pressure or use of non-invasive ventilator support [BiPAP] for

more than 16 hours per day [Phase I]). No studies have been published evaluating concurrent treatment with nusinersen.

Mendell and colleagues (2017) published data from the Phase I trial on Zolgensma (NCT02122952). The study involved the infusion of a single dose of the therapy in individuals with genetically confirmed SMA type 1 and 2 copies of SMN2 who experienced onset of symptoms between birth and 6 months of age. To be eligible for participation, individuals were required to have hypotonia, a delay in motor skills, poor head control, round shoulder posture and joint hypermobility. Exclusion criteria included presence of active viral infection (HIV, hepatitis B or C), invasive ventilatory support or with pulse oximetry less than 95% saturation, persistent anti-AAV9 antibody titer (≥ 1:50), concomitant illness that in the opinion of the Principal Investigator created unnecessary risks for gene transfer, concomitant use of drugs for treatment of myopathy or neuropathy, drugs used to treat diabetes mellitus, or ongoing immunosuppressive therapy or immunosuppressive therapy within 3 months of starting the trial, abnormal clinically significant laboratory values (GGT > 3XULN, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.8 mg/dL, Hgb < 8 or > 18 g/Dl; WBC > 20,000 per cmm), and signs of aspiration based on a swallowing test with an unwillingness to use an alternative to oral feeding.

In the Phase I trial, individuals received 1 of 2 doses of AVXS-101, 6.7 x $10^{13}$ vg/kg (low-dose) or 2.0 x $10^{14}$ vg/kg (high-dose). The low-dose cohort included 3 individuals who were treated at a mean age of 6.3 months (range, 5.9 to 7.2 months) whereas the high-dose cohort included 12 individuals treated at a mean age of 3.4 months (range, 0.9 to 7.9 months). All but 1 individual in the high-dose cohort were treated prior to 6 months of age. Mean age of symptom onset ranged from 0 to 3 months. Concomitant treatment with Spinraza (nusinersen) did not occur during the study. The primary study outcome was safety in terms of the rate of treatment-related serious adverse events (SAEs) that were grade 3 or higher. The primary efficacy endpoint was time until death or the need for permanent ventilatory assistance, which was defined as needing ventilation at least 16 hours a day for at least 14 consecutive days. The secondary efficacy outcome was change in the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders (CHOP INTEND) score, a 16-item 64-point scale that assesses motor function and attainment of significant developmental milestones including the ability to sit unassisted and roll over unassisted. Maintenance of scores over 40 points on the CHOP INTEND is considered to be clinically meaningful for individuals with SMA (Mendell, 2017).

As reported by Mendell and colleagues (2017), at the data cutoff of August 7, 2017 all 15 individuals were alive and without need for permanent ventilator assistance at 20 months of age (compared with a historical rate of survival of 8%). At baseline, none of the individuals in the low-dose cohort had achieved any motor milestones and

individuals in the high-dose cohort had not achieved any motor milestone other than bringing a hand to the mouth. As of August, 2017, the majority of individuals in the high-dose cohort, and none in the low-dose cohort had achieved at least one major motor milestone. A total of 11 individuals in the high-dose cohort sustained CHOP INTEND scores of more than 40 points. Earlier gene therapy infusion appeared to be associated with higher changes in scores for motor function as assessed by CHOP INTEND scores. A single study participant was older than 6 months of age at study entry (7.9 months); this individual achieved the fewest major milestones assessed in the study cohort. A total of 56 SAEs were observed in 13 individuals. Of these, two events were considered treatment-related; both involved elevated levels of aspartate aminotransferase (ALT) and aspartate aminotransferase (AST). Mendell et al. (2017, supplemental materials) noted that evidence from neurophysiological and animal studies supports the mechanistic importance of therapeutic intervention before motor neuron death, and hence emphasizes the importance of early intervention with Zolgensma to rescue neurons.

Two-year follow-up data on the 12 individuals in the Phase I trial who received high-dose therapy were reported by Al-Zaidy and colleagues in 2019b. At the final evaluation, 7 of the 10 individuals who did not need ventilator support prior to study participation still did not need ventilator support. The other 3 individuals, who did require ventilator support at the end of the study, had experienced early symptom onset in the first month of life and rapid disease progression. Of the 5 of 12 individuals who required ventilator support at the final follow-up, none met the criteria for needing permanent ventilator assistance. Six of the 7 individuals who were able to feed orally at baseline continued to do so at the end of the study. At the final follow-up, 11 individuals were able to swallow and at least partially feed orally compared with 7 individuals at baseline. Major motor milestones achieved included full head control and the ability to sit unassisted in 11 of 12 participants. All of the 11 individuals could sit for at least 5 seconds, 10 sat unassisted for at least 10 seconds and 9 sat unassisted for at least 30 seconds. Nine individuals were able to roll and 2 of the 12 were able to crawl, stand and walk independently. The 12 individuals experienced an average of 1.4 respiratory hospitalizations per year (range 0 to 4.8). No additional data on the rate of grade 3 or higher adverse events were reported in this publication.

Al-Zaidy (2019a) compared outcomes in the 12 participants in the Phase I trial with a prospective natural history cohort consisting of 16 individuals age ≤ 6 months at age of enrollment with SMA1 and 2 copies of SNM2 who were enrolled in the NeuroNext natural history study (NN101). None of the participants in the gene therapy group died before the 24-month follow-up whereas 8 (50%) of those in the natural history cohort died at a mean of 8.9 months. All 12 individuals in the gene therapy cohort achieved and maintained clinically significant improvements in motor function compared with none in the natural history cohort. In the gene therapy cohort, the mean CHOP-

INTEND score was 28.2 at baseline, 50.0 at 12 months and 56.5 at 24 months. In the natural history cohort, these scores were 20.3, 10.1 and 5.3, respectively.

Mendell and colleagues (2020) reported five-year follow-up in a long-term extension of the Phase I trial. A total of 13 of the original 15 individuals were enrolled in the extension study, all 3 members of the low-dose cohort and 10 of 12 individuals from the high-dose cohort. At the data cutoff date for this publication, maximum follow-up was 6.2 years after treatment. At least 1 SAE was reported in 8 individuals (62%), 1 from the low-dose cohort and 7 from the high-dose cohort. The most frequently reported SAEs acute respiratory failure (4 events), pneumonia (4 events), dehydration (3 events), respiratory distress (2 events) and bronchiolitis (2 events). All SAEs were considered by investigators to be unrelated to Zolgensma therapy. At a mean follow-up time of 5.2 (range, 4.6 to 6.2) years after dosing, all 3 individuals in the low-dose cohort were alive and 2 of these were not on permanent ventilation. All 10 individuals in the high-dose cohort were alive and did not require permanent ventilation. In the high-dose cohort, all motor milestones that were previously attained were maintained and 2 of the 10 attained a video-confirmed motor milestone of standing with assistance. As of the data cutoff date, 7 of the 13 individuals were receiving concomitant nusinersen.

A Phase III open-label single-arm trial known as STRIVE, conducted at multiple sites in the United States, was published in 2021 by Day and colleagues. The trial evaluated the dosage used in the commercial onasemnogene abeparvovec-xioi product, which was the higher dose used in the Phase 1 trial. Trial inclusion criteria included age less than 6 months at enrollment and a diagnosis of SMA type 1 with 1 or 2 copies of SMN2. Exclusion criteria include the following: Persistent anti-AAV9 antibody titer > 1:50 , pulse oximetry with less than 96% saturation at screening while the individual is awake or asleep without any supplemental oxygen or respiratory support, non-invasive ventilatory support averaging ≥ 6 hours daily over the 7 days prior to the screening visit; or at least 6 hours/day on average during the screening period or requiring ventilatory support while awake at any point prior to dosing, presence of active viral infection (HIV, hepatitis B or C, or Zika virus), serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening, upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening, severe non-pulmonary/respiratory tract infection within 4 weeks before administration of gene replacement therapy or concomitant illness that creates unnecessary risks for gene replacement therapy such as major renal or hepatic impairment, known seizure disorder, diabetes mellitus, idiopathic hypocalcuria or symptomatic cardiomyopathy, concomitant use drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis or immunomodulators within 3 months prior to gene replacement therapy or clinically significant abnormal laboratory values (gamma glutamyl-

transpeptidase [GGT], ALT, and AST > 3 × ULN, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.0 mg/dL, hemoglobin [Hgb] < 8 or > 18 g/dL; white blood cell [WBC] > 20,000 per cmm) prior to gene replacement therapy. Co-primary outcomes were survival at 14 months of age and ability to sit for at least 30 seconds at 18 months of age. Survival was defined as the absence of death or permanent ventilation, with ventilation defined as tracheostomy or at least 16 hours a day of non-invasive non-perioperative ventilation support for at least 14 days in situations where there was no acute reversible illness.

A total of 22 individuals were enrolled in the STRIVE trial at a mean age of 3.7 months (standard deviation [SD], 1.6 months). Before treatment, none of them required non-invasive ventilator (NIV) support and all were able to feed exclusively orally and swallow thin liquids. At 18 months of age, 13 of 22 (59%) individuals achieved the co-primary endpoint of independent sitting for at least 30 seconds. An additional individual was able to sit for at least 30 seconds at the 14-month visit, but was uncooperative at 18 months. For the other co-primary endpoint, 20 of 22 (91%) individuals survived without permanent ventilation at 14 months. Mean increases from baseline in the CHOP INTEND score were 11.7 points at 3 months and 14.6 points at 6 months. At some timepoint in the study, 21 individuals (95%) achieved a CHOP INTEND score of at least 40 points, which the authors noted is unusual for children with SMA type 1. One enrolled individual died of respiratory distress; the death was considered to be unrelated to treatment. Three participants had treatment-related SAEs, two cases of elevated hepatic aminotransferases and one case of hydrocephalus.

In 2021, Mercuri and colleagues published findings of the phase III STRIVE-EU, conducted at several centers in Europe. Eligibility criteria were similar to the U.S. STRIVE study, described above. However, individuals requiring non-invasive ventilatory support for less than 12 hours a day or who required feeding support, were included in STRIVE-EU. The primary outcome, independent sitting for at least 10 seconds at any study visit up to 18 months of age, also differed from the U.S. STRIVE study. There was a secondary outcome of ventilation-free survival at 14 months, with the same definition of permanent ventilation as the U.S. STRIVE study. The study enrolled and dosed 33 individuals at a mean age of 4.1 months. At baseline, 9 of 33 individuals (27%) required ventilator support, 9 (27%) received feeding support and 5 (15%) received both ventilator and feeding support. One individual was excluded from the intention to treat (ITT) analysis due to being dosed at 181 days. A total of 14 of 32 individuals (44%) in the ITT analysis achieved the primary endpoint of functional independent sitting for at least 10 seconds. The endpoint was achieved at a median age of 15.9 months. For the secondary outcome, 31 of 32 individuals (97%) survived free from permanent ventilator support at 14 months. As in the U.S. STRIVE study, study participants achieved improvements in the CHOP INTEND score. Mean improvement in scores from baseline were 10.3 points at 3 months and 13.6 points at 6 months, and 24 individuals (73%) achieved a CHOP INTEND score of at least 40

points. One death occurred among study participants and this was determined to be unrelated to treatment. A total of 32 participants (97%) had at least one adverse event and 6 (18%) participants had a treatment-related SAE.

Strauss and colleagues published findings of the Phase III single-arm SPRINT study in individuals with a genetic diagnosis of SMA and no clinical evidence of disease (i.e., presymptomatic). Study findings were published separately for the individuals with two (2022a) and three (2022b) copies of SMN2 (2022b). Children with the SMN2 gene modifier variant (c.859 G>C) (which is associated with a milder disease course) could enroll in the study, but those with the SMN2 gene modifier variant would not be included in the ITT population. None of the 29 infants enrolled (14 in the 2-copy cohort and 15 in the 3-copy cohort) had a c.859 G>C modifier variant. Participants received a one-time single infusion of onasemnogene abeparvovec at no later than 6 weeks of age. All participants took oral prednisolone starting at least 1 day prior to infusion to attenuate the inflammatory response to AAV9. The primary efficacy outcome was the ability to sit for at least 30 seconds through 18 months of age in the 2-copy cohort and the ability to stand independently for at least 3 seconds at up to 24 months of age in the 3-copy cohort. In the 2-copy cohort, the secondary endpoints were survival at 14 months, defined as the avoidance of death or avoidance of requiring permanent ventilation (tracheostomy or at least 16 hours daily respiratory assistance for at least 14 consecutive days in the absence of an acute reversible illness, excluding in the perioperative period) and the ability to maintain body weight at or above the 3rd percentile at all visits without the need for feeding support at any visit up to 18 months. In the 3-copy cohort, the secondary efficacy endpoint was the ability to walk alone at any visit up to 24 months, and exploratory endpoints were survival at 14 months of age and the ability to maintain body weight at or above the 3rd percentile without the need for feeding support at any visit up to 24 months. Findings were compared to those of children in the historical Pediatric Neuromuscular Clinical Research (PNCR) cohort which described the natural course of SMA type 1.

As reported by Strauss (2022a), the 14 infants in the 2-copy cohort were infused with onasemnogene abeparvovec at a median of 21 days of life (range, 8 to 34 days). All 14 of them achieved the primary efficacy endpoint of independent sitting for at least 30 seconds at any visit up to 18 months of age. None of the children in the historical PNCR cohort achieved this milestone. Of the 12 children who were assessed at the 18-month visit, all were able to sit independently for at least 30 seconds at that visit. In terms of secondary endpoints, all 14 children were alive and free of permanent ventilation at 14 months (compared with 6 of 23 in the historical PNCR cohort). None of the children in the cohort required any type of mechanical respiratory support during the trial. Thirteen of the 14 children maintained a body weight at or above the 3rd percentile without the need for feeding support throughout the trial. There were a total of 159 treatment-emergent adverse events (TEAEs); each participant experienced at least 1 TEAE and 5 reported a serious TEAE. Ten children had a TEAE considered by the investigator to be related to the

study treatment and none of these was serious. Of the TEAE of special interest, 3 children experienced hepatotoxicity, 3 experienced thrombocytopenia, 2 experienced a cardiac adverse event, 3 experienced sensory abnormalities suggestive of ganglionopathy and 2 experienced thrombotic microangiopathy. The investigator considered only 2 events, thrombocytopenia and platelet count decrease, as possibly related to treatment and both events were resolved within a week.

Strauss (2022b) reported on the 15 infants in the 3-copy cohort of the SPRINT trial. All participants were infused with onasemnogene abeparvovec at a median of 32 days of life (range, 9 to 43 days). All 15 children achieved the primary efficacy endpoint for this cohort, which was independent standing for at least 3 seconds at any visit up to 24 months of age. This milestone was achieved at a median age of 377 days, and all children retained this milestone at the 23-month study visit. In comparison, in the historical PNCR cohort only 24% of children with SMA achieved independent standing. Fourteen of the 15 (93%) children walked independently for at least five steps up to 24 months, compared with 21% of children in the PNCR cohort. Participants walked independently at a median age of 422 days. None of the children in the 3-copy cohort required mechanical respiratory support of any kind throughout the trial. There were a total of 166 TEAEs; each participant experienced at least 1 TEAE and 3 children reported a serious TEAE. Eight children (53%) had a TEAE considered by the investigator to be related to the study treatment and none of these was serious. Of the TEAE of special interest, 4 children experienced hepatotoxicity, 2 experienced thrombocytopenia, 3 experienced a cardiac adverse event and 1 experienced a sensory abnormality suggestive of ganglionopathy. The investigator considered all of the hepatotoxicity events to be related to treatment and considered the cardiac adverse events to be possibly or probably related to treatment.

Other published studies include a retrospective case series reported on a single U.S. state's clinical experience with Zolgensma (Waldrup, 2020). The study included 21 children between the ages of 1 and 23 months old who met FDA eligibility criteria. The FDA criteria do not specify number of SMN2 copies; in this sample, SMN2 copies ranged from 2 to 4. A total of 16 participants had symptomatic SMA and 5, who were identified through the state's newborn screening program, were asymptomatic. Age at symptom onset was not provided, but the age at dosing with Zolgensma ranged from 1 month to 23 months. After treatment, 2 of the 9 children under 6 months old, both of whom had been presymptomatic, had elevations in AST and ALT, with or without a concurrent GGT elevation. In both cases, the elevations were deemed related to suboptimal prednisolone administration. Among the 12 children age 8 months or older at treatment, 8 (67%) had elevations in AST and/or ALT and 6 of these also had elevations in GGT. None of the children had symptomatic liver dysfunction. In the sample as a whole, 19 of 21 children (90%) had a decline in platelet count on day 7 after transfer; none required treatment and all returned to a normal value by day 14. Of the 19 children who completed at least 2 functional assessments (most with CHOP-

INTEND), 17 (89%) improved by at least 1 point on functional outcome measures by 4 months after treatment and 12 (70%) improved by at least 3 points.

No published randomized controlled trials (RCT) have compared treatment with onasemnogene abeparvovec-xioi and nusinersen. In 2021, Bischof and colleagues published a matched indirect comparison between these 2 treatments in symptomatic individuals with SMA type 1. Pooled independent patient data (IPD) from the START and STRIVE-US trials (total n=34) were used to evaluate onasemnogene abeparvovec-xioi and aggregate data from the nusinersen arm of a clinical trial called SHINE was used to evaluate nusinersen data (n=81). The authors used complex data analysis techniques to account for differences in the data for the two treatment approaches. The analysis found a significantly lower event-free survival with onasemnogene abeparvovec-xioi compared with nusinersen (Hazard Ratio [HR], 0.19, 95% CI, 0.07 to 0.54). There was not a statistically significant difference between the onasemnogene abeparvovec-xioi versus nusinersen groups in the rate of overall survival (HR, 0.35, 95% CI, 0.02 to 1.32). Between 6 and 18 months, there was not a statistically significant difference between groups in the proportion of individuals who could sit unassisted for at least 30 seconds. At 18 months, individuals receiving onasemnogene abeparvovec-xioi were significantly more likely (at the 95% CI level, not the 99% CI level) than those in the nusinersen group to be able to sit independently (relative risk [RR], 2.79, 95% CI, 1.13 to 6.89).

The published clinical trials use a single dose of gene therapy. Zolgensma is expected to represent a one-time treatment, given that development of AAV antibodies following gene therapy may limit the possibility of re-dosing or re-treating individuals. In the Phase I trial, one subject did not pass screening owing to the presence of anti-AAV9 antibody. Given that re-treatment may not be possible, establishing treatment durability and appropriate patient selection is important.

There are a number of open questions regarding Zolgensma therapy for SMA. The long-term durability of Zolgensma remains unknown, with the longest follow-up reported in published studies currently being five years. While the magnitude of treatment effect induced by Zolgensma appears sufficient to result in clinically meaningful motor function (as represented by a 40-point threshold as evaluated by the CHOP INTEND scores), it does not appear that treatment of individuals with SMA type 1 restores them to a healthy, non-diseased phenotype. Additional data are also being gathered about short-term and long-term safety of Zolgensma. Acute serious liver injury, including acute liver failure resulting in death has been reported in children following treatment with Zolgensma Treatment of individuals with SMA types 2 and 3 also remains under investigation; given the relatively stable clinical course of SMA types 2 and 3, with outcome differences related to the number of SMN2; additional

SMN expression in older SMA patients is less likely to have a significant clinical effect (Mendell, 2017 supplemental materials). Given that SMA is an irreversible, neurodegenerative disease, gene therapy may have a greater therapeutic impact early in the disease process. Also, given that the gene transfer viral doses for older individuals based on body weight is much greater, risks associated with larger dosing remain unknown (Mendell, 2017 supplemental materials).

In 2020, a working group within CURE SMA, a non-profit patient advocacy organization, published a letter to the editor recommending expansion of the criteria for SMA treatment (Glascock, 2020). The working group recommended immediate treatment of infants diagnosed with SMA via newborn screening who have up to four copies of survival motor neuron gene 2 (SMN2), based on the premise that individuals with three or four copies of SMN2 demonstrate a variable disease phenotype. Limited data (Feldkotter et al., 2002) suggests that a minority of individuals with four copies of SMN2 may develop a SMA phenotype consistent with SMA type 1 or 2 (1.6% and 14%, respectively), whereas about 5% of individuals with three SNM2 copies develop type 1 disease (60% develop type 2 and 35% develop type 3 disease) (Cusco, 2020). However, disease-modifying treatment (including Zolgensma) for pre-symptomatic SMA infants with four copies of SMN2 remains unstudied, and there are no data available to assess the potential benefits and harms of such treatment in this group of individuals. Onset of SMA-associated signs and symptoms before 6 months of age, irrespective of SMN2 copy number, is currently consistent with the Position Statement noted above.

## Background/Overview

Spinal muscular atrophy (SMA) is a neuromuscular disorder that is characterized by degeneration of motor neurons of the spinal cord and brainstem. This degeneration results in progressive muscle weakness and atrophy. Atrophy occurs especially in the muscles that control the mouth, throat and respiration. Common complications of SMA include growth failure, restrictive lung disease, scoliosis, joint contractures and sleep disorders (Prior, 2016). SMA is the most common genetic cause of childhood death.

SMA is most often (96% of cases) caused by mutations in the survival motor neuron 1 (SMN1) gene, located on chromosome 5q13.2, which lead to deficiency in SMN protein (Verhaart, 2017). The inheritance pattern of chromosome 5q-related SMA is autosomal recessive. The different forms of 5q-SMA are caused by biallelic deletions or mutations in the SMN1 gene on chromosome 5q13.2. The most common mutation of the SMN1 gene is a deletion of exon 7; approximately 94 percent of individuals with clinically typical SMA carry homozygous deletions of exon 7. While the most common forms of SMA are caused by deletions or mutations in the SMN1 gene

on chromosome 5q, there are a number of rare genetically and clinically heterogeneous non-5q spinal muscular atrophies. The SMN2 gene, which is nearly identical to the SMN1 gene, produces a low level (approximately 10%) of full-length function SMN protein and can modify the severity of SMA (Parente, 2018). The number of SMN2 copies ranges from zero to five, and the presence of three or more copies has been found to correlate with a milder form of SMA (Prior, 2016). Individuals with SMA type 1 are predicted to have two copies of the SMN2 gene (Butchbach, 2006). Defects in SMN2 alone do not appear to cause SMA (Verhaart, 2017). However, the correlation between the copy number of the SMN2 gene and the phenotype is not an exact correlation and may be related to other phenotypic modifiers, such as the presence of the variants c.859G>C in exon 7 and A-44G, A-549G, and C-1897T in intron 6 of SMN2 that act as positive modifier. For example, a case series of 450 Brazilian subjects found that those with specific pathogenic variants (c.460C>T and c.5C>G) presented a milder phenotype, and the SMN2 copy number did not correlate with disease severity (Mendonça, 2020).

The clinical phenotype of SMA ranges from mild to severe. SMA type 0 is most severe and SMA type 4 is least severe. SMA type 1 (also known as Werdnig-Hoffman disease) is the most common type representing about 60% of SMA diagnoses.

Table 1: Clinical Classification of Spinal Muscular Atrophy

| SMA Type | Age of Onset | Highest Achieved Motor Function | Life Expectancy |
|---|---|---|---|
| 0 | Prenatal | None | < 6 months |
| 1 | < 6 months | Sit with support | < 2 years |
| 2 | 6-18 months | Sit independently | > 2 years |
| 3 | > 18 months | Stand and walk | Adult |
| 4 | > 10 years | Walk during adulthood | Adult |

Adapted from Verhaart, 2017

The incidence of SMA is approximately 1 in 10,000 births (Parente 2018; Verhaart, 2017). Incidence rates by SMA type are estimated at 5.5, 1.9 and 1.7 per 100,000 births for SMA type 1, 2 and 3, respectively (Verhaart, 2017). The prevalence of all types of SMA is about 1 to 2 per 100,000. Due to the short life expectancy, the prevalence of SMA type 1 is approximately 0.04 to 0.28 per 100,000. The prevalence of SMA type 2 and SMA type 3 combined is estimated at about 1.5 per 100,000 (Verhaart, 2017). The median survival time for individuals with SMA type 1

is 7.4 months and, in pathophysiological studies, younger age of onset was significantly predictive of earlier death (Farrar, 2013).

Until recently, SMA was diagnosed clinically when individuals presented with symptoms such as hypotonia (low muscle tone) and weakness. With the advent of genetic testing, newborn screening for SMA has become more common and, on July 2, 2018, it was added to the list of newborn screening tests recommended by the U.S. government (HRSA, 2018). Individual states, however, make the final decision on whether or not to add SMA screening to their newborn panels. Prenatal carrier screening for SMA is also available but the degree of uptake is not clear.

A 2007 international consensus statement discussed standards of care for individuals with SMA (Wang, 2007). At that time, no SMA-specific treatments were available and the primary approach to care was managing manifestations of the disease. This includes acute and chronic respiratory illness management (e.g. immunization, airway clearance, non-invasive ventilation), nutrition management (e.g. supplementation, gastrostomy), orthopedic care (e.g. orthotics, mobility aids, orthopedic surgery) and palliative care.

The first medication specifically developed for SMA, nusinersen (Spinraza) was approved by the FDA in 2016. Nusinersen, administered intrathecally (injected into the spine), is an SMN2-directed antisense oligonucleotide (ASO) designed to treat SMA caused by chromosome 5q mutations by increasing production of full-length SMN protein (Spinraza product label, 2016). Subsequently, the oral medication Evrysdi (risdiplam), an SMN2 splicing modifier, was approved by the FDA in August 2020 as a treatment of SMA in individuals aged 2 months and older (Risidiplam product label, 2020).

Gene replacement therapy introduces or alters genetic material to replace the function of a missing or dysfunctional gene with the goal of lessening or eliminating a disease process that results from genetic dysfunction. A gene may be altered using a carrier or "vector" which is often, but not always, a virus that has been modified to remove disease-causing genes, or DNA may be changed using genome (gene) editing, a group of technologies that allows genetic material to be added, removed, or altered. There are different approaches to gene therapy including replacing a mutated gene with a healthy gene, inactivating a mutated gene not functioning correctly, or introducing a new gene. Gene therapy has been under development for decades, but has suffered many setbacks over the years.

AveXis (a Novartis company) has developed a gene therapy called Zolgensma to treat SMA type 1. The therapy uses a non-replicating adeno-associated virus (AAV) as a vector. A functional copy of the SMN1 gene is inserted

into the vector and the therapy is delivered intravenously. The goal of therapy is to induce SMN expression in the treated individual's motor neurons. Zolgensma is able to cross the blood-brain barrier where it targets motor neuron cells (the therapeutic target of most interest, as well as other central nervous system neurons at all regions of the spinal cord); however, Zolgensma can affect any tissue in the body. This may be of interest, given that the SMN protein is expressed by all cells and SMA1 affects multiple systems (e.g., autonomic and enteric nervous systems, cardiovascular system, and pancreas), along with many cell types (e.g., heart, pancreas, and skeletal muscle); however, the clinical significance of inducing SMN expression outside the central nervous system is unknown.

Uncertainty remains regarding the extent to which gene therapy represents a permanent "cure". There are also general uncertainties regarding long-term effectiveness and safety that pertain to gene replacement strategies as a therapeutic class.

*Warnings and Precautions*

Warnings from the FDA PI Label (2021) include the following:

- Thrombocytopenia: Monitor platelet counts before ZOLGENSMA infusion, and weekly for the first month and then every other week for the second and third month until platelet counts return to baseline. (2.3, 5.2)
- Thrombotic Microangiopathy (TMA): If clinical signs, symptoms and/or laboratory findings occur, consult a pediatric hematologist and/orpediatric nephrologist immediately to manage as clinically indicated. (5.3)
- Elevated Troponin-I: Monitor troponin-I before ZOLGENSMA infusion, and weekly for the first month and then monthly for the second and third month until troponin-I level returns to baseline. (2.3, 5.3)

In addition, the Zolgensma label includes the following boxed warning:

- Acute serious liver injury and elevated aminotransferases can occur with ZOLGENSMA. (5.1)
- Patients with pre-existing liver impairment may be at higher risk. (8.6)
- 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. (2.1) (2.3)

Furthermore, the label notes:

- 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.

Use in Specific Populations

Pediatric use: Use of ZOLGENSMA in premature neonates before reaching full term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development. Delay ZOLGENSMA infusion until full-term gestational age is reached. (8.4)

## Definitions

Adeno-associated virus (AAV): A small virus that infects humans and is not known to cause disease. Modified (non-replicating) AAVs are frequently used as viral vectors for gene therapy.

Autosomal recessive disorder: An inherited condition for which two copies of an abnormal gene must be present in order for the disease or trait to develop.

Gene replacement therapy: A medical treatment that introduces or alters genetic material to replace the function of a missing or dysfunctional gene with the goal of lessening or eliminating a disease process that results from genetic dysfunction.

SMN1 and SMN2: Genes that provide instructions for making the survival motor neuron (SMN) protein.

SMA Type 1: also known as infantile spinal muscular atrophy or Werdnig-Hoffmann disease. Onset of symptoms typically presents after birth but before age 6 months. Individuals with SMA type 1 have defects in the SMN1 gene and are predicted to have two copies of the SMN2 gene.

## Coding

*The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. 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.*

~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~



This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

**When services may be Medically Necessary when criteria are met:**

**HCPCS**

| | |
|---|---|
| J3399 | Injection, onasemnogene abeparvovec-xioi, per treatment, up to $5x10^{15}$ vector genomes [Zolgensma] |

**ICD-10 Diagnosis**

| | |
|---|---|
| G12.0 | Infantile spinal muscular atrophy, type 1 [Werdnig-Hoffman] |
| G12.1 | Other inherited spinal muscular atrophy |

**When services are Investigational and Not Medically Necessary:**
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

## References

**Peer Reviewed Publications:**

1. Al-Zaidy SA, Kolb SJ, Lowes L, et al. AVXS-101 (onasemnogene abeparvovec) for SMA1: comparative study with a prospective natural history cohort. J Neuromuscul Dis. 2019a; 6(3):307-317.
2. Al-Zaidy, Pickard AS, Kotha K, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. Pediatr Pulmonol. 2019b; 54(2):179-185.
3. Bischof M, Lorenzi M, Lee J et al. Matching-adjusted indirect treatment comparison of onasemnogene abeparvovec and nusinersen for the treatment of symptomatic patients with spinal muscular atrophy type 1. Curr Med Res Opin. 2021 2021; 37(10):1719-1730.
4. Butchbach ME. Copy number variations in the survival motor neuron genes: implications for spinal muscular atrophy and other neurodegenerative diseases. Front Mol Biosci. 2016; 3:7.
5. Day JW, Finkel RS, Chiriboga CA et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol. 2021; 20(4):284-293.
6. Farrar MA, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol. 2017; 81(3):355-368.

7. Farrar MA, Vucic S, Johnston HM, et al. Pathophysiological insights derived by natural history and motor function of spinal muscularatrophy. J Pediatr. 2013; 162(1):155-9.
8. Feldkötter M, Schwarzer V, Wirth R et al. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet. 2002; 70(2):358-368.
9. Glascock J, Sampson J, Connolly AM, et al. Revised recommendations for the treatment of infants diagnosed with spinal muscular atrophy via newborn screening who have 4 copies of SMN2. J Neuromuscul Dis. 2020; 7(2):97-100.
10. Mendell JR, Al-Zaidy SA, Lehman KJ, et al. Five-year extension results of the Phase 1 START trial of Onasemnogene Abeparvovec in spinal muscular atrophy. JAMA Neurol. 2021; 78(7):834-841.
11. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Eng J Med. 2017; 377(18):1713-1722.
12. Mendonça RH, Matsui C Jr, Polido GJ et al.Intragenic variants in the *SMN1* gene determine the clinical phenotype in 5q spinal muscular atrophy. Neurol Genet. 2020; 6(5):e505.
13. Mercuri E, Muntoni F, Baranello G et al. STR1VE-EU study group. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy type 1 (STR1VE-EU): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol. 2021; 20(10):832-841.
14. Parente V, Corti S. Advances in spinal muscular atrophy therapeutics. Ther Adv Neurol Disord. 2018; 11:1756285618754501.
15. Strauss KA, Farrar MA, Muntoni F et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial. Nat Med. 2022a; 28(7):1381-1389.
16. Strauss KA, Farrar MA, Muntoni F et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial. Nat Med. 2022b; 28(7):1390-1397.
17. Verhaart IEC, Robertson A, 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.
18. Waldrop MA, Karingada C, Storey MA et al. Gene therapy for spinal muscular atrophy: safety and early outcomes. Pediatrics. 2020; 146(3):e20200729.
19. Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol. 2007; 22(8):1027-1049.

**Government Agency, Medical Society, and Other Authoritative Publications:**

~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~



This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

1. Cuscó I, Bernal S, Blasco-Pérez L et al. Practical guidelines to manage discordant situations of SMN2 copy number in patients with spinal muscular atrophy. Neurol Genet. 2020; 6(6):e530.
2. Health Resources and Services Administration (HRSA). Recommended uniform screening panel. Available at: https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html. Accessed on August 1, 2022.
3. Prior TW, Finanger E. Spinal Muscular Atrophy. Last updated 12/2020. In: Adam MP, Ardinger HH, Pagon RA et al., Editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from http://www.ncbi.nlm.nih.gov/books/NBK1352. Accessed on August 1, 2022.
4. Risdiplam product label. Last updated 8/2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213535s000lbl.pdf. Accessed on August 1, 2022.
5. Spinraza product label. Last updated 12/2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf. Accessed on August 1, 2022.
6. U.S. National Library of Medicine ClinicalTrials.gov. Available at: https://www.clinicaltrials.gov/. Accessed on August 1, 2022.
7. Zolgensma product label. Last updated 2021. Available at: https://www.fda.gov/media/126109/download. Accessed on August 1, 2022.

## Websites for Additional Information

1. National Organization for Rare Disorders (NORD). Spinal Muscular Atrophy. Available at: https://www.rarediseases.org/rare-diseases/spinal-muscular-atrophy/. Accessed on August 1, 2022.
2. U.S. National Library of Medicine Genetics Home Reference. Spinal Muscular Atrophy. Available at: https://medlineplus.gov/genetics/condition/spinal-muscular-atrophy/ Accessed on August 1, 2022.

## Index



**The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.**

## Document History

| Status | Date | Action |
|---|---|---|
| Revised | 09/06/2022 | Medical Policy & Technology Assessment Committee (MPTAC) review. Removed text regarding SMA type from MN statement. |
| Revised | 08/11/2022 | ~~Medical Policy & Technology Assessment Committee (~~MPTAC~~)~~ review. Changed MN criterion to "no more than 3 copies of SMN2." Rationale, Background/Overview and References sections updated. |
| Reviewed | 11/11/2021 | MPTAC review. Rational, Background/Overview and References sections updated. |
| Revised | 11/05/2020 | MPTAC review. In MN statement, changed "6 months of age or younger" to "2 years of age or younger" and removed criterion on use of nusinersen (Spinraza). Removed second MN statement relating to age at time of FDA approval of onasemnogene abeparvovec-xioi. Rationale and References sections updated. |
| Reviewed | 05/14/2020 | MPTAC review. Rationale and References sections updated. Updated Coding section with 07/01/2020 HCPCS changes; added J3399 replacing J3490 NOC code. |
| Revised | 07/29/2019 | MPTAC review. Modified bullet F in first medically necessary statement and added second medically necessary statement. |
| New | 06/06/2019 | MPTAC review. Initial document development. |