Zolgensma® (Onasemnogene Abeparvovec-Xioi)

Policy Number: IEXD0079.10
Effective Date: December 1, 2025

➲ Instructions for Use

Table of Contents **Page**

Applicable States 1
Coverage Rationale 1
Applicable Codes 2
Background 3
Benefit Considerations 3
Clinical Evidence 3
U.S. Food and Drug Administration 7
References 7
Policy History/Revision Information 8
Instructions for Use 8

Related Policies

None

Applicable States

This Medical Benefit Drug Policy applies to Individual Exchange benefit plans in all states except for Massachusetts, Nevada, and New York.

Coverage Rationale

➲ See Benefit Considerations

Zolgensma is proven and medically necessary for one treatment per lifetime for the treatment of spinal muscular atrophy (SMA) in patients who meet all of the following criteria:

- Submission of medical records (e.g., chart notes, laboratory values) confirming the mutation or deletion of genes in chromosome 5q resulting in one of the following:
  - Homozygous gene deletion or mutation of survival motor neuron 1 (SMN1) gene (e.g., homozygous deletion of exon 7 at locus 5q13); **or**
  - Compound heterozygous mutation of SMN1 gene [e.g., deletion of SMN1 exon 7 (allele 1) and mutation of SMN1 (allele 2)]

  and
- **One** of the following:
  - Diagnosis of symptomatic SMA by a neurologist with expertise in the diagnosis of SMA; **or**
  - **Both** of the following:
    - Diagnosis of SMA based on the results of SMA newborn screening; **and**
    - Submission of medical records (e.g., chart notes, laboratory values) confirming that patient has four copies or less of SMN2 gene

  and
- For use in a neonatal patient born prematurely, the full-term gestational age has been reached; **and**
- Patient is less than 2 years of age; **and**
- Patient is not dependent on **either** of the following:
  - Invasive ventilation or tracheostomy
  - Use of non-invasive ventilation beyond use for naps and nighttime sleep

  and
- Zolgensma is prescribed by a neurologist with expertise in the treatment of SMA; **and**

- Patient is not to receive routine concomitant SMN modifying therapy [e.g., Evrysdi (risdiplam), Spinraza (nusinersen)] (patient's medical record will be reviewed and any current authorizations for SMN modifying therapy will be terminated upon Zolgensma approval); **and**
- Patient does not have an elevated anti-AAV9 antibody titer above 1:50; **and**
- Patient will receive prophylactic prednisolone (or glucocorticoid equivalent) prior to and following receipt of Zolgensma in accordance with the United States Food and Drug Administration (FDA) approved Zolgensma labeling; **and**
- Patient will receive Zolgensma intravenously in accordance with the FDA approved labeling; **and**
- Patient has never received Zolgensma treatment in the patient's lifetime; **and**
- Provider does not request a planned inpatient admission for the sole purpose of administering Zolgensma; **and**
- Authorization will be issued for no more than one treatment per lifetime and for no longer than 45 days from approval or until 2 years of age, whichever is first

Additional Information Relevant to the Review Process but Not Impacting the Determination of Medical Necessity

- Physician attests that the patient, while under the care of the physician, will be assessed by **one** of the following exam scales during subsequent office visits†
  - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scale during subsequent office visits while the patient is 2 to 3 years of age or younger; **or**
  - Hammersmith Functional Motor Scale Expanded (HFMSE) during subsequent office visits while the patient is 2 to 3 years of age or older

  and
- Physician attests that the patient will be assessed via the CHOP INTEND scale to establish a baseline functional assessment within the following timelines†
  - For patients greater than 2 months of age at the time of Zolgensma administration, a baseline CHOP INTEND score will be assessed within the two weeks prior to Zolgensma administration; **or**
  - For patients less than or equal to 2 months of age at the time of Zolgensma administration, a baseline CHOP INTEND score will be assessed within the two weeks prior to, or the two weeks following Zolgensma administration

†For quality purposes only, this information will not be considered as part of the individual coverage decision.

Zolgensma is not proven or medically necessary for:
- The treatment of pre-symptomatic patients diagnosed by newborn screening who have more than four copies of the SMN2 gene; **or**
- The treatment of symptomatic later-onset SMA older than 2 years of age; **or**
- SMA without chromosome 5q mutations or deletions; **or**
- The routine combination treatment of SMA with concomitant SMN modifying therapy

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J3399	Injection, Onasemnogene abeparvovec-xioi, per treatment, up to 5×10^{15} vector genomes

Diagnosis Code	Description
G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]
G12.1	Other inherited spinal muscular atrophy
G12.8	Other SMAs and related syndromes
G12.9	Spinal muscular atrophy, unspecified

Background

Spinal muscular atrophy (SMA) is a rare, autosomal recessive neuromuscular disease that affects the survival of motor neurons of the spinal cord. SMA is caused primarily by biallelic (homozygous) variants in the SMN1 gene. The estimated annual incidence of SMA is 5.1 to 16.6 cases per 100,000 live births. Approximately 1/40 to 1/60 people are SMA carriers, equating to 3.5 to 5.2 million and 12 to 18 million individuals in the United States and Europe, respectively. SMA is characterized by the degeneration of motor neurons of the spinal cord, resulting in hypotonia and muscle weakness. Historically, SMA has been classified into five phenotypic subtypes (0-4) based on age of symptom onset and motor function achieved. The uncommon SMA type 0 phenotype has prenatal onset associated with decreased fetal movement, significant motor weakness, respiratory distress, difficulty feeding, contractures, and cardiac defects noted at birth. The most incident phenotype, type 1 SMA, occurs in approximately 60% of infants born with SMA with weakness during the first 6 months and never achieving independent sitting. SMA type 2 phenotype has been defined by weakness between 6 and 18 months of life after achieving independent sitting but not walking independently. Approximately 10% of individuals born with SMA presented with SMA type 3 and achieved walking independently with abnormal gait and were diagnosed after 18 months of age. An estimated < 1% of individuals with SMA present during adulthood (usually fourth decade) and are classified as type 4 or adult-onset SMA and have mild motor impairment. Although symptoms are milder and progression is slower, people with adult-onset SMA often experience a long process of testing and evaluations before diagnosis. Current literature indicates that the number of copies of the SMN2 gene that a patient has is the best predictor of clinical phenotype. Individuals with more SMN2 copies usually have a less severe form of SMA than those with fewer copies.

Zolgensma (Onasemnogene abeparvovec) is a one-time SMN1 gene replacement therapy that treats the root cause of SMA, deletion or loss of function of the SMN1 gene, by delivering a copy of the human SMN gene via an adeno-associated virus serotype 9 (AAV9), which crosses the blood-brain barrier. Zolgensma is designed with a self-complementary DNA structure and a continuous promoter that allows for immediate and sustained expression of SMN protein, providing a rapid onset of effect. Motor neurons are non-dividing cells; thus a stable SMN gene supplemented via a viral vector would not expected to be lost as children grow, potentially allowing for long-term, sustained SMN protein expression with a one-time dose, and providing a durable therapeutic effect. The 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. Zolgensma infusion is to be delayed until full-term gestational age is reached.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the member specific benefit plan document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

Type 1 SMA

A phase 1, open-label, single site, dose-escalation study (CL-101) evaluated the safety and efficacy of a one-time IV administration of Zolgensma in 15 patients with type 1 SMA with two copies of survival motor neuron 2 (SMN2) 9 months of age or younger who developed symptoms of SMA prior to 6 months of age. Three of the patients received a low dose (6.7×10^{13} vg per kilogram of body weight), and 12 received a high dose (2.0×10^{14} vg per kilogram). The dosage received by patients in the low-dose cohort was one-third of the dosage received by patients in the high-dose cohort. However, the precise dosages of Zolgensma received by patients in this completed clinical trial are unclear due to a change in the method of measuring Zolgensma concentration, and to decreases in the concentration of stored Zolgensma over time. The retrospectively estimated dosage range in the high-dose cohort is approximately 1.1×10^{14} to 1.4×10^{14} vg/kg. The primary outcome was safety. The secondary outcome was the time until death or the need for permanent ventilatory assistance. As of the data cutoff for the manuscript publication on August 7, 2017, all 15 patients were alive and event-free at 20 months of age, as compared with a rate of survival of 8% in a historical cohort. In the high-dose cohort, a rapid increase from baseline in the score on the CHOP INTEND scale followed gene delivery, with an increase of 9.8 points at one month and 15.4 points at three months, as compared with a decline in this score in a historical cohort. Of the 12 patients who had received the high dose, 11 sat unassisted, nine rolled over, 11 fed orally and could speak, and two walked independently. Elevated serum aminotransferase levels occurred in four patients and were attenuated by prednisolone.

A follow up presentation of the CL-101 study showed that at all patients were alive and without the need for ventilation at 24 months. In the high dose cohort (cohort 2), all patients achieved at least one motor milestone with 11 of 12 achieving motor milestones rarely seen in the type 1 SMA population. All 11 patients who achieved these milestones were 6 months of age or less at the time of gene therapy administration. The one patient not experiencing advanced motor milestone achievement was 8 months of age at the time of gene therapy administration. Patients treated with Zolgensma had a marked, early, and rapid improvement in CHOP-INTEND score, in contrast with untreated SMA type 1 patients who experienced a 10.7-point drop in CHOP-INTEND scores from 6–12 months of age. At 24 months follow-up, patients had a mean CHOP-INTEND score increase of 25.4 points from baseline (n = 12). The maintenance of scores of more than 40 points on the CHOP-INTEND scale has been considered to be clinically meaningful in SMA. Eleven of 12 patients achieved and maintained a score > 40 points for a mean of 19.5 months. In contrast, one recent natural history study reported that SMA type 1 children neither achieve nor maintain CHOP-INTEND scores > 40 points after 6 months of age. None of the patients in the low dose cohort were able to sit without support, or to stand or walk; in the high dose cohort, 9 of the 12 patients (75.0%) were able to sit without support for ≥ 30 seconds, and two patients (16.7%) were able to stand and walk without assistance. As of April 2018, the oldest subject in cohort 2 was 46.2 months of age with 40.6 months of follow-up.

A pivotal, Phase 3, multicenter, open-label trial (STRIVE) is currently underway evaluating the safety and efficacy of a one-time intravenous administration of Zolgensma in patients less than 6 months of age with type 1 SMA based on genetic confirmation of a bi-allelic mutation of the SMN1 gene with one or two copies of the SMN2 gene who are not dependent on invasive or non-invasive ventilatory support for greater than six hours a day. Enrollment in the study is complete with 22 patients with two copies of SMN2 receiving Zolgensma. The patient population and baseline characteristics closely match those studied in the CL-101 study. The mean baseline age was 3.7 months with a range of 0.5-5.9 months. The mean baseline CHOP-INTEND score was 32 (range 17-52). As of March 2019, 19 of 20 patients (95%) who had reached 10.5 months of age survived without permanent ventilation and 13 of 15 patients (87%) who had reached 13.6 months of age were surviving without permanent ventilation. The average increase in CHOP-INTEND scores were 6.9, 11.7, and 14.3 at months 1, 3, and 5 respectively. Twenty-one of 22 (95%) patients achieved CHOP-INTEND score of 40 or greater. Eleven of 22 (50%) patients were able to sit without support at a mean age of 13.8 months. No patient screened for AAV9 antibodies had exclusionary AAV9 antibody titers.

Pre-Symptomatic Patients Likely to Develop Type 1 SMA

A phase 3, multicenter, open-label trial (SPR1NT) is currently underway evaluating the safety and efficacy of a one-time intravenous administration of Zolgensma in patients less than 6 weeks of age with SMA based on a genetic confirmation of a bi-allelic mutation of the SMN1 gene with two or three copies of the SMN2 who have yet to develop symptoms who have a baseline compound muscle action potential (CMAP) > 2 mV at baseline. Enrollment is underway with planned enrollment of at least 27 patients in cohorts with two and three copies of SMN2. Patients are to receive a one-time intravenous administration of Zolgensma at a dose on 1.1×10^{14} vg per kg.

As of June 11, 2020, 29 patients have received Zolgensma in the trial with positive interim results. All patients were alive and free of ventilatory support at median age at follow up of 15 months. All patients fed orally and did not require feeding tube support of any kind.

Among the cohort of patients with two copies of SMN2, 11 of 14 patients (79%) achieved the study's primary endpoint of sitting without support for at least 30 seconds. Ten of these patients achieved this within the WHO window of normal development. Five patients (36%) could stand independently, three of whom achieved this milestone within the WHO window of normal development. Four patients (29%) could walk independently, three of whom achieved this milestone within the WHO window of normal development. All patients achieved CHOP INTEND scores of ≥ 50, and 13 (93%) achieved a CHOP INTEND score ≥ 58.

Among the cohort of patients with three copies of SMN2, eight patients (53%) achieved the study's primary endpoint of standing alone for at least three seconds, and six patients (40%) walked independently. These motor milestones were all achieved within the WHO window of normal development. Of those patients who had not yet achieved these milestones, all were still within the WHO window of normal development. All patients had steady gains in mean raw score of Bayley-III fine and gross motor scales.

Prediction of SMA Phenotype Based on SMN2 Copy Number

As stated above, current literature indicates that the number of copies of the SMN2 gene that a patient has is the best predictor of clinical phenotype, however the correlation is not absolute. A recent publication assessed the correlation of SMN2 copy number to SMA phenotype in 3,459 patients worldwide from reports published after 1999. Analysis of the North American cohort showed similar findings. Seventy-three percent of patients of patients with two copies were diagnosed with type I SMA, accounting for 79% of all type I SMA cases. Patients with three copies of SMN2 were the most numerous in the entire cohort accounting for approximately half of the cases. Fifteen percent of patients with three copies of SMN2 were diagnosed with Type I SMA. Ninety-five percent of patients with type II SMA and 54% of patients with type III SMA had three copies or less of SMN2. Approximately 15% of patients in the worldwide cohort had four copies of SMN2. Patients with four copies of SMN2 were highly unlikely to be diagnosed with type I SMA as greater than 99% of cases were diagnosed with non-type I SMA, with approximately 90% of patients with four SMN2 copies developing type III SMA. Patients with four copies or more of SMN2 accounted for 0.3% of all cases diagnosed with type I SMA and approximately 5% of all cases diagnosed with type II SMA.

Type 2 SMA

A phase 1, multicenter, open-label, dose-escalation trial (STRONG) is currently underway evaluating the safety and efficacy of a one-time intrathecal administration of onasemnogene abeparvovec in patients with SMA based on a genetic confirmation of a bi-allelic mutation of the SMN1 gene with three copies of SMN2, who are able to sit but cannot stand or walk at the time of study entry with onset of SMA symptoms occurring before 12 months of age. These patients would be classically considered patients with likely type 2 SMA. Patients will receive onasemnogene abeparvovec in a dose comparison safety study of two potential therapeutic doses (3 patients at each dose). Patients will be stratified in two groups, those < 24 months of age at time of dosing and those ≥ 24 months and < 60 months of age at time of dosing. Fifteen patients < 24 months (cohort 1) will be enrolled and twelve patients ≥ 24 < 60 months (cohort 2) will be enrolled. The first cohort will enroll three patients (cohort 1) < 24 months of age who will receive intrathecal administration of 6.0 x 10^{13} vg of onasemnogene abeparvovec (Dose A). After review of the data from cohort 1 by the Data Safety Monitoring Board (DSMB), a determination will be made to advance to Dose B, in which three patients less than 60 months of age will receive 1.2 x 10^{14} vg of onasemnogene abeparvovec intrathecally. After review of the data from cohort 1 by the Data Safety Monitoring Board (DSMB), a determination will be made to advance to Dose C, in which three patients from cohort 2 will receive 2.4 x 10^{14} vg of onasemnogene abeparvovec intrathecally. Three patients in cohort 1 received dose A. Based on demonstrated acceptable safety, three additional patients in cohort 2 received dose B. Given ongoing demonstration of acceptable safety, 13 additional patients in cohort 1 and 9 in cohort 2 were treated with dose B. Primary endpoints were safety/tolerability, optimal dose, ability to stand unsupported ≥ 3 sec (cohort 1), and Hammersmith Functional Motor Scale-Expanded score (cohort 2). As of March 2019, 30 patients have been enrolled and received intrathecal onasemnogene abeparvovec. Interim data from this multicenter study showed improvements in motor function in patients with type 2 SMA. 44% of patients in cohort 1 gained motor milestones following treatment. 25% of patients in cohort 2 gained motor milestones following treatment. In patients greater than 24 months of age, the mean increase in HFMSE was 4.2 points after an average therapy duration of 7.5 months. In cohort 2, 50% of patients experienced a 3 point or greater increase in HFMSE after 1 month of treatment. No dose limiting toxicity was observed, permitting dose-escalation to dose C (2.4 x 10^{14} vg) in two patients aged less than 24 months. On October 30, 2019, the FDA placed partial hold on clinical trials for intrathecal administration of onasemnogene abeparvovec based on findings from a pre-clinical study in which animal findings showed dorsal root ganglia mononuclear cell inflammation, sometimes accompanied by neuronal cell body degeneration or loss. The partial hold did not apply to any intravenous onasemnogene abeparvovec clinical trials.

Professional Societies

Health Care Provider Working Group

An SMA working group of American and European health care providers updated the SMA best practice recommendations for diagnosis through systematic literature review and sequential modified Delphi surveys and discussions. The Health care provider working group (HCPWG), supported by Cure SMA, included 18 members plus 2 organizing and nonvoting Cure SMA staff members who moderated discussions and had no stake in the decisions. The HCPWG included 5 European physician neurologists, 12 US physician neurologists, and 1 U.S. genetic counselor. All HCPWG members participated voluntarily without compensation. Included in their recommendations was a recommendation that SMA infants identified by NBS and before treatment initiation should be characterized by SMN2 copy number, current motor function, age at symptom onset, and severity of symptoms. The classification of SMA severity based on SMA type has changed due to the effectiveness of SMN-enhancing treatments in tandem with early identification by NBS and urgent confirmatory diagnosis. Thus, the HCPWG discussed that classification of newborns by SMA type is not clinically meaningful for newly diagnosed infants with SMA and those treated early in their life with SMN-enhancing treatment(s). Because SMN2 copy number is associated with disease phenotype, progression, and outcomes, determining the number of SMN2 copies is urgent and should be included as a component of the confirmatory diagnostic testing to include both the number of SMN1 and SMN2 gene copies. In addition, based on consensus recommendations by US clinicians to treat infants with 4 copies of SMN2 urgently, distinguishing between 4 and 5 copies of SMN2 is necessary.

2024 European Neuromuscular Expert Consensus Statement on Gene Replacement Therapy for Spinal Muscular Atrophy

In 2020, a group of 13 European neuromuscular experts, conveyed to help aid the rational use of Zolgensma and presented 11 consensus statements covering qualification, patient selection, safety considerations and long-term monitoring after the European Medical Agency (EMA) approval of Zolgensma. After three years, a similar yet larger group of European experts assembled to assess the emerging evidence of onasemnogene abeparvovec's role in treating older and heavier SMA patients, integrating insights from recent clinical trials and real-world evidence. This effort resulted in 12 consensus statements, with strong consensus achieved on 9 and consensus on the remaining 3, reflecting the evolving role of onasemnogene abeparvovec in treating SMA. The following are recommendations from the European expert panel:

- **Consensus statement 1**: Traditional SMA types (e.g., type 0, 1, 2, 3, 4) alone are not sufficient to define patient populations who might benefit most from gene therapy. In symptomatic patients age at onset, disease duration and motor function status at the start of treatment are the most important factors that predict response to treatment.
- **Consensus statement 2**: In truly presymptomatic patients SMN2 copy number is the most important predictor of clinical severity and age of onset. As long as no better biomarkers or predictors are available, treatment decisions for presymptomatic patients should primarily be based on SMN2 copy number. Determination of SMN2 copy number needs to be performed in an expert laboratory with adequate measures of quality control.
- **Consensus statement 3**: An important aspect to consider when assessing the possibilities to treat with onasemnogene abeparvovec older and heavier patients compared to the younger, lighter, and less chronic patients, is that while the risk-benefit ratio for those younger age group is well documented from multiple published studies, there is still limited data on the efficacy of onasemnogene abeparvovec in the older and heavier population. In this patient population it is particularly important for physicians to discuss with families the fact that the risk-benefit ratio is still unknown, and to carefully manage parents' or patients' expectations.
- **Consensus statement 4**: In patients presenting symptoms at birth, treated after a long disease duration, or with already severe evolution, parents should be clearly made aware that despite the use of gene therapy there is a high risk of living with a very severe disability. Palliative care should be discussed as an alternative treatment option in these circumstances.
- **Consensus statement 5**: Since the risk of gene therapy increases with the dose administered and since the dose is proportional with the weight and age, heavier and older patients should be treated very cautiously as the data available in these patients are very scarce. Treatment with other disease-modifying treatments or future intrathecal administration of onasemnogene abeparvovec if it shows an acceptable efficacy-safety ratio, should be considered as a valuable alternative, and discussed with parents.
- **Consensus statement 6**: In absence of convincing evidence of published superiority of the combination of two disease-modifying treatments (e.g., gene therapy and nusinersen; or gene therapy and risdiplam), combinatorial therapies cannot be recommended at the moment. A controlled clinical trial setting with head-to-head-comparison of one vs. two disease-modifying treatments is regarded as gold-standard to answer this open question.
- **Consensus statement 7**: Centers performing gene therapy for SMA should have broad expertise in the assessment and treatment of SMA according to international standards. They should also have the ability and resources to deal with potential side effects of gene therapy. Personnel should be trained and have experience in the use of standardized and validated outcome measure for SMA to document treatment effects.
- **Consensus statement 8**: There is convincing evidence that early initiation of any disease-modifying treatment, ideally in the presymptomatic stage of the disease, is associated with markedly better outcome as compared to later start of treatment. In newly diagnosed patients, including those identified by NBS, any delay of treatment should be avoided. Ideally, the time frame between diagnosis and initiation of a disease-modifying treatment should be the shortest possible. Patients with SMA type 1 and/or 2 copies of *SMN2* should be considered medically urgent.
- **Consensus statement 9**: Data concerning effectiveness and safety should be collected systematically for all patients treated. Treatment centers should be provided with adequate resources to perform long-term monitoring of treated patients with standardized outcome measures. Where available disease specific registries should be used for data collection to allow comparison between different treatments. Data analysis should be performed primarily by academic institutions and networks.
- **Consensus statement 10**: Based on the currently available data and in light of existing effective treatment alternatives, intravenous gene replacement therapy with onasemnogene abeparvovec for older and heavier patients should only be performed under a rigorous protocol with continuous monitoring of safety and efficacy. Treatment of patients above 21 kg cannot be recommended.

- **Consensus statement 11**: As the use of Zolgensma will generate additional evidence during the coming years, pharmaceutical industry, regulators, patient representatives, and academic networks should collaborate to ensure that any new data on effectiveness and safety are publicly available in an unbiased and timely manner. This growing body of evidence is indispensable for an improved risk-benefit assessment for future patients and should not be hampered by particular commercial or academic interests.
- **Consensus statement 12**: SMA should be included in newborn screening programs in countries where at least one disease-modifying treatment is readily available. Patients identified by newborn screening should be evaluated by a pediatric neurologist experienced with neuromuscular diseases as soon as possible. These patients require careful clinical evaluation and assessment of additional biomarkers (e.g., *SMN2* copy number). As soon as either symptoms or low *SMN2* copy numbers (≤ 3) are detected, disease-modifying treatment should be initiated without any delay.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Zolgensma (onasemnogene abeparvovec-xioi) is an adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.

Limitations of Use

- The safety and effectiveness of repeat administration of Zolgensma have not been evaluated.
- The use of Zolgensma in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

References

1. Zolgensma [package insert]. Bannockburn, IL; Novartis Gene Therapies, Inc. February 2025.
2. Markowitz JA, Singh P, Darras BT. Spinal Muscular Atrophy: A Clinical and Research Update. Pediatric Neurology 46 (2012) 1-12.
3. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of > 72,400 specimens. Eur J Hum Genet 2012; 20:27-32.
4. Prior TW, Snyder PJ, Rink BD, et al. Newborn and carrier screening for spinal muscular atrophy. Am J Med Genet A. 2010 Jul;152A (7):1608-16.
5. Lunn MR, Wang CH. Spinal muscular atrophy. Lancet. 2008 Jun 21;371(9630):2120-33.
6. Calucho M, Bernal M, 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. Neuromuscular disorders. 2018; 28:208-15.
7. 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.
8. Protocol for: 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. DOI: 10.1056/NEJMoa1706198.
9. Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. Journal of Neuromuscular Diseases. 2018; 5:145-158.
10. Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1 (STR1VE) Clinicaltrials.gov website https://clinicaltrials.gov/ct2/show/NCT03306277?term=AVXS-101&rank=5. Accessed September 12, 2025.
11. Pre-Symptomatic Study of Intravenous AVXS-101 in Spinal Muscular Atrophy (SMA) for Patients With Multiple Copies of SMN2 (SPR1NT). Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03505099?term=AVXS-101&rank=1. Accessed September 12, 2025.
12. Study of Intrathecal Administration of AVXS-101 for Spinal Muscular Atrophy (STRONG). Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03381729?term=AVXS-101&rank=3. Accessed September 12, 2025.
13. Tse V, Moller-Tank S, Asokan A. Strategies to circumvent humoral immunity to adeno-associated viral vectors. Exper Opin Biol Ther. 2015;15(6):845-55.

14. Glascock J SJ, Haidet-Phillips A, et al. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. Journal of Neuromuscular Diseases. 2018;5(2):145–158.
15. Appendix: Supplementary material for Calucho M, Bernal M, 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. Neuromuscular disorders. 2018; 28:208-15. https://doi.org/10.1016/j.nmd.2018.01.003.
16. 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. Journal of Neuromuscular Diseases. 2020; vol. Pre-press, no. Pre-press, pp. 1-4, 2020. https://doi.org/10.3233/JND-190468.
17. Kirschner J, Butoianu N, Goemans N, et al. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. European Journal of Paediatric Neurology. 2020, doi: https://doi.org/10.1016/j.ejpn.2020.07.001.
18. A Study of Nusinersen Among Participants With Spinal Muscular Atrophy Who Received Onasemnogene Abeparvovec-xioi ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT04488133?term=nusinersen&draw=2&rank=1. Accessed September 12, 2025.
19. Schroth M, Deans J, Arya K, et al. Spinal Muscular Atrophy Update in Best Practices: Recommendations for Diagnosis Considerations. Neurol Clin Pract. 2024;14(4):e200310. doi:10.1212/CPJ.0000000000200310.
20. Kirschner J, Bernert G, Butoianu N, et al. 2024 update: European consensus statement on gene therapy for spinal muscular atrophy. Eur J Paediatr Neurol. 2024;51:73-78. doi:10.1016/j.ejpn.2024.06.001.

Policy History/Revision Information

Date	Summary of Changes
12/01/2025	**Coverage Rationale** • Revised coverage criteria; added criterion requiring the provider does not request a planned inpatient admission for the sole purpose of administering Zolgensma **Supporting Information** • Updated *Background*, *Clinical Evidence*, and *References* sections to reflect the most current information • Archived previous policy version IEXD0208.09

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.