Molina Clinical Policy
Zolgensma (onasemnogene abeparvovec)
Policy No. 348

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OVERVIEW

This policy reviews the use of Zolgensma for the treatment of Spinal Muscular Atrophy (SMA).

Spinal Muscular Atrophy (SMA) is an inherited disorder characterized by progressive degeneration of the spinal cord and brainstem motor neurons. Degeneration of motor neurons leads to muscle atrophy, hypotonia and in severe cases, early death (Zhang et al. 2020). SMA has an autosomal recessive inheritance pattern. It is estimated that SMA affects 1 in 8,000 to 10,000 people worldwide (Keinath et al. 2021). Severe forms of SMA are the number one genetic cause of infant mortality.

SMA is caused by a defect in the survival motor neuron 1 (*SMN1*) gene, with nearly all cases resulting from deletion, rearrangement, or mutation in the SMN1 gene. Pathogenic changes in SMN1 result in significantly lower levels of functional SMN protein, leading to loss of motor neurons. There is significant variation in SMA clinical presentation (Cure SMA, 2018). Part of this variability is due to another gene that can modify the effect of pathogenic mutations in the SMN1 gene. The modifier gene is called the SMN2 gene. The SMN2 gene sequence is very similar to the SMN1 gene and a normal SMN protein is occasionally made from the SMN2 gene. That small percentage of normal SMN protein made from the SMN2 gene is what modifies the effect of the loss of the SMN1 gene function. The total number and function of SMN2 copies present are inversely correlated with phenotypic severity; a greater number of SMN2 copies provides protection and reduces the severity of the disease. Historically, SMA has been divided into sub-types (SMA types 0, 1, 2, 3, and 4) based on disease onset and severity. The severity correlates with the level of SMN protein. One of the most severe forms of SMA, Type I (Werdnig-Hoffman disease), typically results in death or the need for permanent breathing support by 2 years of age without treatment (MDA.org). An overview of the different subtypes is available in the "Supplemental Information" section of the policy (Table 1). The life expectancy of SMA patients is inversely related to the age of onset, with higher mortality rates associated with early disease onset. SMA is associated with multiple progressive clinical problems affecting respiration, nutrition, and neuromuscular function. The leading cause of morbidity and mortality in SMA types 1 and 2 is respiratory failure. Prior to approval of disease-modifying therapies, the focus of treatment has been on supportive care for symptomatic and related clinical problems (Prior et al. 2024). Following the introduction of new disease modifying therapies such as zolgensma, nusinersen, and risdiplam, the mortality rate of individuals with SMA has dropped by 77% from 2014 to 2024 (ICER 2025).

Zolgensma (onasemnogene abeparvovec; formerly AVXS-101) was approved by the FDA in 2019 for the treatment of children under the age of two who have SMA and bi-allelic mutations in SMN1. The indication includes all SMA patients; however, the risks of therapy in older children and adults is a concern given toxicities of high viral doses needed in these age groups.

Zolgensma is a single dose treatment that targets the root cause of SMA by delivering a fully functional SMN gene into target motor neurons. This gene therapy uses a viral vector, that is a non-replicating, recombinant, adeno-associated virus, serotype 9 (AAV9). AAV9 is a naturally occurring virus. Because of its presence in nature some pediatric patients may have already been exposed to AAV viruses and developed antibodies against this virus. If AAV9 antibodies are present at high levels, patients may be ineligible for Zolgensma treatment due to the risk of

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severe immunologic reactions on repeat exposure to the AAV9 capsid (part of the Zolgensma viral vector). It is reported that in 150+ patients intended to be treated with Zolgensma, only 5% were excluded due to AAV9 antibody titers greater than 1:50 (Novartis 2019).

Current FDA labeling (FDA label, 2025) includes a **black box warning** noting reports of acute serious liver injury, acute liver failure, and elevated aminotransferases. In addition, there have been cases of acute liver failure that led to fatalities. Patients with preexisting liver impairment may be at high risk. Other adverse events (AEs) include thrombocytopenia, elevated blood creatine phosphokinase, elevated troponin, croup, lethargy, and hypercalcemia.

RELATED POLICIES

Molina Pharmacy Policy: C20580-A: Evrysdi (risdiplam)
MCP- 293: Spinraza (nusinersen)
MCP-478: Itvisma

COVERAGE POLICY

All Gene Therapy requests require Molina Medical Director review.

Zolgensma (onasemnogene abeparvovec) gene therapy for the treatment of SMA may be **considered medically necessary** when ALL the following clinical criteria are met:

1. Prescribed by, or in consultation with, a board-certified pediatric neurologist, neuromuscular specialist or neurologist with experience in the diagnosis and management of SMA
2. Definitive diagnosis of spinal muscular atrophy (SMA) defined by genetic testing
3. Genetic testing confirms bi-allelic mutations (chromosome 5q related deletion or point mutations) in the survival motor neuron 1 (SMN1) gene documented by the presence of ONE of the following:
    a. Homozygous deletions of SMN1 gene (e.g., homozygous deletion of exon 7 at locus 5q13)
    b. Homozygous mutation in the SMN1 gene (e.g., biallelic mutations of exon 7)
    c. Compound heterozygous mutation in the SMN1 gene [e.g., deletion of SMN1 exon 7 (allele 1) and mutation of SMN1 (allele 2)]
4. Four or fewer copies of SMN2 gene identified by a laboratory assay capable of distinguishing the difference between four copies and five copies of SMN2
5. Less than 2 years of age at time of administration of Zolgensma
    a. For premature neonates: Full-term gestational age must be reached. Documentation required.
    Informational Note: It is not recommended to administer Zolgensma to premature neonates prior to attaining the full-term gestational age because concurrent corticosteroid treatment may impair neurodevelopment. Delay infusion until full-term gestational age has been attained.
6. Member is less than 21 kg. Submit current weight (in kilograms) for determination of dosage
7. Confirmation/attestation of member's current and previous SMA treatments:
    a. Member is not currently enrolled in SMA clinical trials and is ineligible for clinical trial enrollment
    NOTE: Members eligible for, or currently enrolled in, SMA clinical trial enrollment will not be authorized. Individual should receive treatment and monitoring per clinical trial protocols in place by the applicable Institutional Review Board.
    b. Member has not previously received gene therapy, or Zolgensma
    c. Zolgensma will not be used in combination with an investigational treatment or alternative SMA therapy (e.g., Spinraza, Evrysdi). Treatment must be discontinued prior to infusion of Zolgensma

    Molina Clinical Reviewer: Review clinical history and profile; terminate current authorizations for SMN modifying therapy upon approval of Zolgensma.

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8. Baseline motor function assessment using at least ONE of the following assessment tools appropriate for participant age and motor function does not indicate advanced SMA at baseline (e.g., complete paralysis of limbs; permanent ventilation support):
    a. CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
    b. HFMS: Hammersmith Functional Motor Scale
    c. HFMSE: Hammersmith Functional Motor Scale Expanded
    d. Hammersmith Infant Neurologic Exam Part 2 (HINE-2)
    e. 6-minute walk test (6MWT)
    f. Upper Limb Module (ULM) score *(non-ambulatory patients)*

    Refer to 'Supplemental Information' section (Table 2) for additional information on neurological function assessments for motor development. Measures that have been developed and validated specifically for SMA populations include CHOP INTEND, HFMS, HFMSE.

9. Baseline (pre-treatment) laboratory tests within normal limits. Required within 30 days of request.
    a. Liver function: normal clinical exam, and prothrombin time; AST and ALT levels <2 x Upper Limit of Normal, GGT < 3X ULN, bilirubin < 3.0 mg/dL
    b. Hgb > 8 or < 18 g/Dl; WBC < 20,000 per cm]
    c. creatinine < 1.8 mg/dL
    d. Baseline platelet count

10. Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus)

11. Baseline anti-AAV9 antibody titers **less than or equal to** 1:50 prior to infusion, measured using an enzyme-linked immunosorbent assay (ELISA). Documentation required.
    **The safety and efficacy of Zolgensma patients with anti-AAV9 antibody titers above 1:50 have not been evaluated.*

12. Member does **NOT** have advanced SMA, including but not limited to ANY of the following:
    a. Complete paralysis of limbs
    b. Invasive ventilatory support (tracheostomy)
    c. Non-invasive ventilator support (e.g., CPAP, BPAP) for greater than 16 hours/day

13. Member will receive systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg) prior to and following administration of Zolgensma in accordance with the FDA approved Zolgensma labeling

14. Member does not have a known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients

15. Member has not used of any of the following within 3 months of planned Zolgensma therapy: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy (SPR1NT)

CONTINUATION OF THERAPY

Zolgensma is indicated to be dosed and infused one time only. Repeat treatment or re-administration of a dose is not supported by labeling or compendia and is not considered medically necessary.

The safety and effectiveness of repeat administration 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 (FDA Prescribing Information 2025).

DURATION OF APPROVAL: Infusion may be performed up to ONE MONTH from time of authorization OR until 2 years of age, whichever occurs first.

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QUANTITY LIMITATIONS: FDA approved dosing with one-time dose per lifetime. Additional infusions will not be authorized.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Clinical Development Program Overview for Onasemnogene Abeparvovec-xii

PHASE	DESCRIPTION	SMA TYPE	N	STATUS
Infants under 6 weeks (presymptomatic with a genetic diagnosis of SMA and 2 or 3 copies SMN2)				
Phase 3	SPR1NT: Pre-Symptomatic Study of Intravenous AVXS-101 in SMA for Patients with Multiple Copies of SMN2 (NCT03505099)	Type 1 Type 2 Type 3	44	Completed July 15, 2021
Infants under 6 months of age (SMA type I)				
Phase 1	PIVOTAL: Gene Transfer Clinical Trial for SMA Type 1 (NCT02122952)	Type 1	15	Completed Published
Phase 4	START: Long-Term Follow-up Study for Patients from AVXS-101-CL-101; (NCT03421977)	Type 1	15	**Ongoing** Estimated Study Completion Date: December 2033
Phase 3	STR1VE-US: Gene Replacement Therapy Clinical Trial for Patients with SMA Type 1 (NCT03306277)	Type 1	21	Completed Nov 12, 2019
Phase 3	STR1VE-EU Single-Dose Gene Replacement Therapy Clinical Trial for Patients with SMA Type 1 (NCT03461289)	Type 1	30	Completed Sep 11, 2020
Children up to 60 months of age (SMA Type II)				
Phase 1	STRONG: Study of Intrathecal Administration of AVXS-101 for SMA (NCT03381729)	Type 2 Type 3	32	Completed Nov 18, 2021
Phase 4	Trial to evaluate the safety, tolerability and efficacy of OAV101 (AVXS-101) in patients with SMA ≤ 24 months and weighing ≤ 17 kg, over a 18-month period post infusion. NCT05073133	Type 1 Type 2 Type 3	16	Completed August 8, 2023
Phase 3b	To evaluate the safety, tolerability and efficacy of intravenous administration of OAV101 in SMA patients weighing ≥ 8.5 kg and ≤ 21 kg, over a 12 month period. NCT04851873	Type 1 Type 2 Type 3	24	Completed June 13, 2023

Clinical trials for the development of Zolgensma for symptomatic SMA Type 1 include four prospective cohort studies (listed in the Table above): two phase 1 dose-finding studies, two phase 3 confirmatory studies (STRIVE-US; STRIVE EU), and one long-term follow-up study (START).

FDA approval was based on a pooled analysis of the pivotal phase 1 trial (n=15) and STRIVE-US trial (n=21) with a data analysis cut off March 2019. Efficacy was established looking at the endpoints of survival, and achievement of developmental motor milestones (for example, sitting without support). Comparison of the results of the ongoing clinical trial to available natural history data of patients with infantile-onset SMA was the primary evidence for the effectiveness of Zolgensma.

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Pivotal Trial (NCT02122952). Zolgensma was studied in an open-label trial of 15 infants with SMA who had homozygous SMN1 exon 7 deletions. The patients were randomly assigned to receive either a single high-dose (n = 12) or a low-dose (n = 3) of onasemnogene abeparvovec intravenously. At 20 months, all 15 patients were alive and did not require permanent mechanical ventilation, whereas the historical control group's rate of survival without permanent ventilation was only 8%. Motor function improved in the high-dose Zolgensma cohort compared to the historical controls. In contrast to historical controls, a number of treated infants attained motor milestones such as sitting unassisted (n = 11), oral feeding (n = 11), rolling over (n = 9), and walking independently (n = 2). The authors concluded that in patients with SMA type 1, a single intravenous infusion of AAV vector containing DNA coding for SMN1 resulted in longer survival, superior achievement of motor milestones, and better motor function than in historical cohorts; however additional research is required to confirm the safety and efficacy of this gene therapy.

START: Long-Term Follow-Up Study (LTFU) (NCT03421977) is an ongoing, observational, follow-up study for continuous safety monitoring for 15 years in patients from the START phase 1 study (May 2014 through December 2017). Participants were symptomatic infants with SMA type 1 and 2 copies of SMN2 previously treated with an intravenous dose of Zolgensma (low dose, 6.7×10^{13} vg/kg; or therapeutic dose, 1.1×10^{14} vg/kg) in START. Thirteen of 15 original START patients are included in this analysis (n=13; low-dose cohort, n = 3; and therapeutic-dose cohort, n = 10); 2 patients' families declined follow-up participation. Mendell et al. (2021) reported the results of this ongoing study to assess long-term safety (incidence of serious AEs) and durability of response (to determine if developmental milestones attained in the START phase 1 clinical trial were maintained and if new milestones were attained).

The findings indicate that developmental milestones achieved in the phase 1 clinical trial were maintained and new milestones were gained. All 10 patients in the therapeutic-dose cohort survived and did not require continuous ventilation. The five-year extension study results of 13 patients found that all 10 patients in the high-dose group maintained previously acquired milestones without the need for permanent ventilation, while two patients achieved a new milestone of standing with assistance without the addition of nusinersen. It is noted that 7 of the 13 patients later received concomitant nusinersen (all 3 patients in the low-dose cohort and 4 of the 10 patients in the therapeutic-dose cohort) to maximize benefit and not due to a decline in motor function or perceived regression. Six patients in the therapeutic-dose cohort were noted to have received no additional treatment for SMA other than Zolgensma more than four years after administration. The two patients in the therapeutic-dose cohort who met the new START LTFU milestones did not receive nusinersen at any time. The authors concluded that Zolgensma provides sustained and durable efficacy in patients for up to 6.2 years after administration. The anticipated outcomes of completed and ongoing phase 3 and 4 studies will further validate the efficacy and safety of Zolgensma. The STR1VE-US and STR1VE-EU open-label studies provide additional evidence of efficacy (Day et al. 2021; Mercuri et al. 2021). STR1VE-US included 22 patients with infantile-onset SMA (mean age at enrollment 3.7 months) who could feed exclusively by mouth and did not require noninvasive ventilatory support at enrollment (Day et al. 2021); STR1VE-EU enrolled 32 patients with infantile-onset SMA (mean age at enrollment 4.1 months) who required feeding support or noninvasive ventilatory support for less than 12 hours daily, allowing for the inclusion of patients with more severe disease. At 14 months of age, 20 patients (91%) in STR1VE-US and 31 patients (97.5%) in STR1VE-EU survived without the requirement for permanent ventilation, compared to 6 of 23 (26%) in untreated historical controls. At the 18-month trial visit, 13 patients (59%) in STR1VE-US and 14 patients (44%) in STR1VE-EU were able to sit without assistance, whereas none of the 23 untreated historical controls could do so. The results of the phase 3 confirmatory study (STRIVE-US) published after FDA approval were largely consistent with previously available findings at the time of approval.

SPR1NT is a Phase 3, multi-center, single-arm study that investigated the efficacy and safety of Zolgensma in 30 pre-symptomatic children with SMN1 mutations and either 2 or 3 copies of the SMN2 gene who were treated at 6 weeks of age or younger. The trial ended in June 2021. SPR1NT trial participants were divided into 2 cohorts based on SMN2 copy number: Cohort 1 included 14 infants (n=14) with two copies of SMN2 who were **expected** to develop SMA, while Cohort 2 included 15 infants (n=15) with three copies of SMN2 who were **expected** to develop SMA. The trial investigator determined that there were no serious adverse events associated with treatment in either cohort.

SPR1NT clinical trial demonstrates age-appropriate milestone development in pre-symptomatic children with SMA without respiratory or nutritional support of any kind, and with no serious, treatment-related AEs.

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- In the cohort of patients with two copies of SMN2: 11 of 14 (79%) met the study's primary endpoint of sitting without support for at least 30 seconds (10 of these patients did so within the WHO window of normal development); 5 patients (36%) were able to stand independently (3 of whom did so within the WHO window of normal development); 4 patients (29%) were able to walk independently (3 of whom did so within the WHO window of normal development) (Strauss et al., 2022).
- In the cohort of patients with three copies of SMN2, 8 (53%) met the study's primary endpoint of standing alone for at least three seconds, and 6 (40%) walked independently. All these motor milestones were met within the WHO normal development window. All patients who had not yet reached these developmental milestones were still within the WHO normal development window (Strauss et al., 2022).

STRONG is a Phase 1, open-label, dose-comparison, multi-center trial that evaluated the safety and efficacy of a one-time intrathecal (IT) administration of Zolgensma. Patients included in the study were those with SMA type 2 and three copies of the SMN2 gene who were able to sit unassisted for 10 seconds but were unable to walk or stand. The primary endpoints were safety/tolerability, independent standing for ≥ 3 seconds in patients aged 6 to < 24 months or change in Hammersmith Functional Motor Scale-Expanded (HFMSE) score in patients aged 24 to < 60 months. Outcomes were compared with those of Pediatric Neuromuscular Clinical Research dataset (PNCR). In May 2019, reported data showed motor function gains and milestone achievements. Two serious treatment-related AEs also occurred, both transaminase elevation. However, the frequency of children with such AEs was lower than that seen with IV administration of Zolgensma. The FDA initiated a partial clinical trial hold in October 2019. In August 2021, the hold was lifted, and the FDA determined that the STRONG study could proceed with IT delivery. However, despite release from clinical hold, the sponsor (Novartis) elected not to enroll more patients. This phase 1 and 2 study ended in November 2021. The results of the Phase 1/2 STRONG study of 32 children aged ≥ 2 years and < 5 years old with SMA Type 2 were reported in 2021, and data was published in 2023, (Finkel et al). Treatment with Zolgensma IT was safe and well tolerated. Older patients (24 to < 60 months) treated with the medium dose had a statistically significant improvement in the Hammersmith Functional Motor Scale Expanded at month 12 and a clinically meaningful response was noted. These study results may help provide information to providers treating older and /or heavier SMA patients that may be at increased risk for adverse events given higher doses of AAV9 required at higher weights.

Further studies are needed to validate the efficacy of IT delivery in SMA type 2. To address this, Novartis is sponsoring **STEER,** a randomized, sham-controlled, double-blind phase 3 study (NCT05089656). STEER will build upon the Phase ½ STRONG study which showed that IT treatment with Zolgensma led to significant increases in HFMSE scores and a clinically meaningful response in older patients ≥2 years and <5 years old with SMA Type 2. The primary objective of STEER is to evaluate the clinical efficacy, safety, and tolerability of a one-time IT dose of OAV-101 in treatment naïve children and young people with Type 2 SMA who are between 2 and 18 years of age, able to sit, but have never walked. The STEER study was completed by April 29, 2025.

Data from the RESTORE registry was recently published by Servais et al. (2024). RESTORE is an ongoing, prospective, multicenter, observational disease registry assessing real-world treatments outcomes for patients with SMA. Reported assessments included pulmonary function, bulbar function and motor function over 37 months from patients with a range of severity. Statistical analysis was not performed on this real-world data set. Clinical care was not consistent across regions and a specific follow up and treatment protocol was not possible. Real world functional outcomes were consistent with clinical trial data including reported CHOP INTEND scores. Adverse events in RESTORE aligned with the safety profile originally reported in clinical trials. Overall onasemnogene was “transformative” for this patient population.

The SMART trial, is a phase 3b, open label, multicenter study (NCT04851873), evaluating 24 children with body weight between 8.5 kg and 21 kg. Participants were divided into three cohorts based on weight: 8.5 – 13kg, 13-17kg and 17-21kg. Each cohort had 7-9 individuals. All participants were symptomatic, most had SMA type 2, three copies of SMN2 and prior treatment. There were no comparator groups, and the age range in symptomatology was variable. Follow-up was 52 weeks. Primary endpoint was safety and secondary was efficacy. No deaths occurred. Transaminitis was prolonged but ultimately resolved with corticosteroids and were asymptomatic. Transient asymptomatic thrombocytopenia was also prevalent. Otherwise, safety profile was similar across weight groups, & overall, no new safety signals. Maintenance or improvement of motor function was observed for most participants suggestive of clinical benefit McMillan et al. (2025).

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A second trial evaluated the use of Zolgensma in Latin Americans with SMA that included heavier patients.. NCT05073133 is a phase 4 Trial to evaluate the safety, tolerability and efficacy of OAV101 (AVXS-101) in patients with SMA ≤ 24 months and weighing ≤ 17 kg, over an 18-month period post infusion. Saute et al. (2025) reported results of 16 patients. Two deaths occurred, one potentially related to Zolgensma, the other was secondary to respiratory infection & was not attributed to treatment. The patient demise was likely related to treatment, weighed 12kg at dosing and was 18 months old. She developed acute liver injury and multi-organ failure. Although there were heavier participants in the trial that did well, the study did not include a breakdown of each participant's weight. The weight cohorts were greater than or less than 8.5Kg. There did appear to be a trend to more serious adverse events in the heavier cohort of patients although this was not noted to be statistically significant. Most patients improved or maintained motor milestones. Of note, the cohort of patients evaluated in this trial may have been more severe than trial participants in NCT04851873.

Regarding combination therapies of SMN2 modifiers & onasemnogene, a systematic review was completed & published by Bemanalizadeh et al. (2025). They concluded combining therapies appeared to be safe but efficacy was not clearly demonstrated. Earlier age of treatment appeared to be more important than combining therapies.

Registry data suggesting motor benefit in those with tracheostomies has been reported (Erbas et al. 2025) however, there are no clear recommendations in this subgroup of patients. Evidence of benefit of treatment in this subgroup is developing but the FDA label maintains the use of Zolgensma is limited for those on permanent ventilation.

National and Specialty Organizations

- A working group comprised of 15 SMA experts including clinicians and geneticists convened to develop treatment guidelines for infants with SMA in 2018 followed by subsequent revision of those guidelines in 2020. The expert group recommended infants diagnosed with SMA via newborn screening who have four SMN2 gene copies receive immediate treatment (discussed below). This recommended revision was based on Biogen's NURTURE clinical trial (Glascock 2020).
- For those infants in which immediate treatment is not recommended, guidelines were developed that outline the timing and appropriate screens and tests to determine the timing of treatment initiation.

The group noted the recent publication of data from Biogen's NURTURE clinical trial demonstrating the dramatic impact of early nusinersen treatment under 6 weeks of age is significantly superior to treatment after 6 weeks of age in patients with two or three copies of SMN2. According to the Working Group, the predicted outcomes for patients with four copies of SMN2 would be similar to those with three copies.

Patients with 5 (or more) SMN2 gene copies should be observed and screened for symptoms. The group acknowledged that current laboratory assays designed to detect SMN2 copy number frequently have difficulty distinguishing high copy numbers of SMN2, and many laboratories report results as 4 or more SMN2 copies, without providing an exact number. As a result, further testing with a laboratory capable of determining the exact SMN2 copy number is recommended.

Other 2020 recommendations remain unchanged from the previous guidelines in 2018.

European Medical Agency (EMA): 2024 European Neuromuscular Expert Ad-Hoc Consensus Statement on Gene Replacement Therapy for SMA. Following the EMA's approval of Zolgensma in May 2020, 11 consensus statements addressing qualification, patient selection, safety concerns, and long-term monitoring were issued by a panel of 13 neuromuscular specialists. Below are the 2024 updated recommendations from the 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.
- Revised consensus statement 3: An important aspect to consider when assessing the possibilities to treat

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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.
- Revised 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
- Revised 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 J. Kirschner et al. European Journal of Paediatric Neurology 51 (2024) 73–78 76 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: Centres 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 measures for SMA to document treatment effects. Recognition as European Reference Centre (www.ern-euro-nmd.eu) or national accreditation as neuromuscular centre of expertise might serve as additional selection criteria.
- Revised 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 of onasemnogene abeparvovec should be collected systematically for all patients treated. Treatment centres 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 treatment regimens. Data analysis should be performed primarily by academic institutions and networks.
- Revised 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 onasemnogene abeparvovec will generate additional evidence during the coming years, pharmaceutical industry, regulators, J. Kirschner et al. European Journal of Paediatric Neurology 51 (2024) 73–78 77 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.
- New 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 paediatric 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.

NOTE: A consensus greater than 95% was considered "strong consensus", between 75 and 95% "consensus", and between 50 and 75% "majority consensus". If less than 50% approved a statement, it was labeled as "no consensus".

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Institute for Clinical Economic Research:
In a report published in September 2025, ICER noted that the use of SMN directed therapy after gene therapy or in combination should only be done in the context of research studies. Jewelfish trial looking at the combination of Risdiplam and onasemnogene was promising. The remainder of the report focused on apitegromab, however that therapy approval was delayed by the FDA.

SUPPLEMENTAL INFORMATION

Clinical Classification of SMA. SMA disease phenotypes are classified according to a scheme developed at the Muscular Dystrophy Association-sponsored International Consortium on SMA in 1991; these phenotypes were modified into five subtypes based on age of onset, inheritance pattern, and maximum motor function achieved. Table 1 adapted from Table 1 of Verhaart et al. 2017; Number of SMN2 copies based on Calucho et al. 2018.

TABLE 1: CLASSIFICATION OF SMA BY TYPE

SMA Type *(Alternative Names)*	**Age at Symptom Onset**	**Maximum Motor Function Achieved**	**Life Expectancy**	**Incidence**	**Affected Gene(s)** (Usual # of SMN copies)
0 *(Congenital, Prenatal SMA)*	Prenatal (30-36 weeks)	Nil; Decreased Fetal Movement	Rarely past 6 months	<1%	**SMN1** (1 SMN2 copy)
1 *(Severe infantile acute; Werdnig-Hoffman disease)*	Birth to 6 months	Cannot sit independently, difficulty breathing	< 2 years	60%	**SMN1** (2 SMN2 copies)
2 *Dubowitz disease*	6 to 18 months	Sit independently, but cannot stand or walk	> 2 years; 25 years (70%)	25%	**SMN1** (2-4 SMN2 copies) *80% have 3 copies*
3 *Kugelberg-Welander disease*	After 18 months	Can stand or walk, but walking, stairclimbing become difficult. Wheelchair assistance usually needed in later life.	Normal	15%	**SMN1** (3-4 SMN2 copies) *95% have ≥ 3 copies*
4 Adult-onset SMA	Adult; 20-30 years	Walk during adulthood; slow decline; Mild to moderate muscle weakness, tremor, twitching in proximal muscles; difficulty breathing	Normal	<1%	**SMN1** (≥ 4 copies) *4-8 SMN2 copies*

Number in bold indicates the predominate copy number

Age of onset is a predictor of the severity of disease and maximal motor function as higher mortality rates associated with early disease onset (Farrar et al. 2017) Onset occurs before 6 months of age in about 60% of affected individuals; these patients usually do not live past 2 years old.

TABLE 2: SELECT NEUROLOGICAL FUNCTION ASSESSMENTS USED IN SMA CLINICAL TRIALS

Measure	Description
Hammersmith Infant Neurologic Exam (HINE Section 2) NOTE: CL-101 did not collect HINE-2 data, and there are no published data reporting HINE-2 scores with Zolgensma treatment.	• Used for assessing various aspects of neurologic function in infants ages 2 months to 2 years • 3 sections, 26 items – Section 1: Neurologic assessment – Section 2: Developmental milestone assessment – Section 3: Behavioral assessment • Section 2 may be used alone – 8 items, scores of 0 to 2, 3, or 4 – Children with SMA1 may score 0 on all 8 items

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Hammersmith Functional Motor Scale, Expanded (HFMSE) NOTE: The STRONG trial collected HFMSE	• Used to evaluate motor function in individuals with later-onset SMA (SMA2 and SMA3) • 33 items • Total score ranges from 0 to 66; lower scores indicate poorer function • Scores in patients with SMA2 or SMA3 may decline over 12 months
Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)	• Used to evaluate motor skills of children with SMA ages ~4 months to 4 years • Includes 16 items to assess motor skills, each graded on a scale of 0 to 4 response (0 for no response, 1 for minimal, 2 for partial, 3 for nearly full, 4 for complete) • Total score ranges from 0 to 64; maximum total score possible is 64; lower scores indicate poorer function • Infants with SMA may score much lower than unaffected infants • A score exceeding 40 is rarely seen in infants with SMA 1 • Has been validated for use in SMA type 1 infants Informational Note: Lower CHOP-INTEND scores lower scores indicate poorer function. Total score ranges from 0 to 64; maximum total score possible is 64; lower scores indicate poorer function. The mean CHOP INTEND score at baseline was 28 (Phase 3 STR1VE-EU trial; data as of Dec 31, 2019)
Motor Function Measure-32 Item (MFM-32)	• Used to evaluate motor function in children and adults with neuromuscular diseases • Assesses 32 items in 3 dimensions (standing and transfers, axial and proximal motor function, distal motor function) • Total score ranges from 0 to 96; lower scores indicate poorer function

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure)

HCPCS (Healthcare Common Procedure Coding System)

Code	Description
J3399	Injection, Onasemnogene abeparvovec-xioi, per treatment, up to $5x10^{15}$ vector genomes

AVAILABLE DOSAGE FORMS: Zolgensma is provided as a customized kit to meet dosing requirements for each patient, with each kit containing two (2) to nine (9) vials of Zolgensma. Dosage is determined by patient weight.

All vials have a nominal concentration of 2.0×10^{13} vector genomes (vg) per mL. Each vial of Zolgensma contains an extractable volume of not less than either 5.5 mL or 8.3 mL.

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

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APPROVAL HISTORY

12/10/2025 Policy revised. Consolidated limitations & exclusions section into main criteria section for clarity. Increased weight based limitation from 13.5kg to 21kg secondary to new trial information. SMART 3b clinical trial data shows patients above 13.5 kg have been safely treated. A second trial (Ofelia) also appears to generally support use in patients weighing more than 13.5kg.

06/11/2025 Policy revised. Removed requirement for baseline troponin per package insert update for Zolgensma dated February 2025. Annual review will remain December 2025.

12/11/2024 Policy revised. Added requirement of Molina Medical Director review, no other changes to indications. Updated Summary of Evidence and References.

12/13/2023 Policy revised. Removed reference to SMA clinical subtype as a criterion. Allowance of 4 copies of SMN2 modifier gene to be present for approval. Added new warning from prescribing information about fatalities related to liver failure. Added criterion CBC to baseline monitoring criterion number 9. Removed outdated references and added updated references to clinical trials. IRO Peer Review December 7, 2023 by a board-certified practicing physician in Neurological Surgery.

01/04/2023 Policy revised. Updated Overview, Coverage Policy, Summary of Evidence and References sections. IRO Peer Review: 11/30/2022. Board-certified practicing physician in Neurological Surgery.
Practicing physician board certified in Neurology. The following criteria were updated:

- #3: No change in intent of criteria; clarification by addition of 'Clarified genetic confirmation of SMA with bi-allelic mutations' (as per indication)
- #4 (copies of SMN2 gene):
  Revised from 'No more than 2 copies of the SMN2 gene' revised to: No more than 3 copies of the SMN gene
- #5: Removed criterion: Less than 6 months of age at the onset of symptoms
- #7 (previous treatments): Revised criteria from 'Confirmation/attestation of member's current and previous enrollment in clinical trials, history of treatment with gene therapy, prior antisense oligonucleotide treatment, or cell transplantation related to SMA or Zolgensma, including:' Revised to: Confirmation/attestation of member's current and previous SMA treatments.
- #7c: Revised criteria to allow for members who are/have been on Evrysdi or Spinraza to receive Zolgensma. Previous criteria only allowed tx-naïve patients.
  - Revised from: Member is not currently receiving therapy with an investigational or commercial product, including Spinraza (nusinersen) or Evrysdi (risdiplam), for the treatment of SMA.
  - Revised to: Zogensma will not be used in combination with an investigational treatment or alternative SMA therapy [e.g., Spinraza (nusinersen), Evrysdi (risdiplam)]. Treatment must be discontinued prior to infusion of Zolgensma].
- #7c: Revised Molina Clinical Reviewer note.
  - Revised from: Molina Clinical Reviewer: May also engage with Prescriber/treating physicians to determine whether switching to Zolgensma therapy may offer a superior chance of clinical benefit.
  - Revised to: Molina Clinical Reviewer: Review clinical history and profile; terminate current authorizations for SMN modifying therapy upon approval of Zolgensma.
- #11: Revised criterion. Broaden criteria to ensure that member does not have advanced SMA (per labeling):
  - Revised from: Member must not currently require permanent ventilation defined by the need for continuous ventilator support (invasive or non-invasive ventilation) for more than 16 hours during a 24-hour period for at least 14 days without an acute, reversible illness: a. Invasive ventilatory support; b. Pulse oximetry < 95% saturation; c. Use of non-invasive ventilation (BiPAP) beyond use for naps and nighttime sleep
  - Revised to: Member does **not** have advanced SMA, including but not limited to *ANY* of the following: a. Complete paralysis of limbs; or b. Invasive ventilatory support (tracheostomy); or c. Non-invasive ventilator support (e.g., CPAP, BPAP) for greater than 16 hours/day
- #12: Added criteria. Member will receive systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg) prior to and following administration of Zolgensma in accordance with the Trial to evaluate the safety, tolerability and efficacy of OAV101 (AVXS-101) in patients with SMA ≤ 24 months and weighing ≤ 17 kg, over a 18-month period post infusion. approved Zolgensma labeling.
- Limitations and Exclusions criteria:
  - Removed (under exclusions): 'ANY of the following concomitant medical condition(s)' and added respiratory exclusions as per labeling in 'experimental, investigational, and unproven' section.
  - Removed (under exclusions): Member's weight: At screening visit is < 2 kg, OR Weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards
  - Revised (under 'experimental, investigational, and unproven'): Revised from 'Prior treatment, or being considered for treatment, with other gene therapy, prior antisense oligonucleotide treatment, or cell transplantation for SMA.' Revised to: 2. Prior treatment, or being considered for treatment, with other gene therapy
  - Removed (under 'experimental, investigational, and unproven'): Type 2 and 3. Clinical evidence for Type 2 and 3 SMA are not available at this time. Clinical trials are currently recruiting (SPRINT trial).
  - Added: Complete paralysis of limbs (FDA approved labeling, 2022)
  - Added: Advanced Spinal Muscular Atrophy (FDA approved labeling, 2022)

12/08/2021 Policy reviewed and updated, no changes in coverage criteria, updated references. Notable content updates include Clinical Trials results.

9/2021 Policy converted to new template.

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Q4 2020 P&T Policy revised. IRO Peer Review: 11/13/2020. Practicing physician board-certified in Neurology, Sleep Medicine.

- Added 'ineligible for clinical trial enrollment' to criteria: 'Member is not currently enrolled in SMA clinical trials and is ineligible for clinical trial enrollment;"
- Added 'newborn screening' to genetic testing criterion
- Added criteria (based on recent consensus): Member is less than 13.5 kg; Member does not have advanced SMA at baseline (e.g., complete paralysis of limbs; lower CHOP-INTEND scores); Two or fewer copies of SMN2 gene
- Updated 'Duration of Authorization' criteria FROM: Infusion may be performed up to 6 months from time of authorization- TO: Infusion may be performed up to ONE month from time of authorization OR until 2 years of age, whichever occurs first;
- Added references to Evrysdi where applicable (in exclusion of concurrent therapy);
- Added the following evidence/guidelines: Hayes assessment report; Update of the Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group with 2020 recommendations (Glascock 2020); The European Neuromuscular Expert Ad-Hoc Consensus Statement on Gene Replacement Therapy for Spinal Muscular Atrophy (Kirschner J, 2020)

6/18/2019 P&T New policy. IRO Peer Review: 6/10/2019. Practicing physician board-certified in Neurology, Sleep Medicine; AND IRO Peer Review: 6/7/2019. Practicing physician board certified in Pediatrics, Neurology with Special Qualification in Child, Neurodevelopmental Disabilities.

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Supplemental Information

Table 1 adapted from Table 1 of Verhaart et al. 2017; Number of SMN2 copies based on Calucho et al. 2018:

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APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

Illinois

For Medicaid reviews, per Illinois Department of Healthcare and Family Services (HFS) as of 1/1/2026, prior authorization criteria must be to FDA-approved label AND include treatment of patients up to and including 4 copies of SMN2 or to not specify a specific number of SMN2 copies. No other restrictions allowed.

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