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

Last Approval: 12/8/2021
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Spinal Muscular Atrophy (SMA) is an autosomal recessive hereditary disease characterized by progressive degeneration of spinal cord and brainstem motor neurons resulting in hypotonia, atrophy of skeletal muscles, and generalized weakness (Zhang, et al. 2020). It is caused by a defect in the survival motor neuron 1 (*SMN1*) gene, with nearly all cases resulting from deletion, rearrangement, or mutation in SMN1 which significantly lower levels of a functioning SMN protein, resulting in a swift loss of motor neurons, the specialized cells that control muscle contraction. Most patients with SMA have homozygous deletion of exon 7 of SMN1 gene located on chromosome 5q13 but maintain ≥ 1 copy of SMN2 gene. Although approximately 95% of patients have the same homozygous deletion of the SMN1 gene, a significant range in clinical presentation/phenotypes exists (Cure SMA, 2018). It is estimated that SMA affects 1 per 8,000 to 10,000 people worldwide (Genetics Home Reference, 2019).

SMA is generally divided into sub-types (SMA types 0, 1, 2, 3, and 4) based on disease onset and severity, usually correlating to levels of SMN protein. The most severe form 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 'Supplemental Information' section of policy (Table 1). 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 clinical problems that affect respiratory, nutritional, orthopedic, rehabilitative, emotional, and social aspects of the disease. The clinical manifestations and disease severity of SMA are highly variable. Prior to the approval of disease modifying therapies, the focus of treatment has been on supportive care, symptomatic and related clinical problems that develop with age including, respiratory, nutritional, and orthopedic management [i.e., pulmonary treatments including airway clearance and if needed, respiratory support; improving sleep quality through nocturnal noninvasive ventilation (often with bi-level positive pressure); optimization of nutritional status; maintenance of fitness and endurance through regular exercise; and occupational therapy to help with management of truncal and limb weakness]. The leading cause of morbidity and mortality in SMA types I and II is respiratory failure.

Disease-Modifying Therapies

Spinraza (nusinersen), an antisense oligonucleotide, controls the mutations caused in the chromosome 5q. This selectively binds and targets RNA and regulates gene expression. It has the potential to enhance the amount of functional SMN protein in infants and children with SMA. Spinraza, the first FDA-approved therapy for SMA (2016), is indicated for the treatment of SMA (any subtype) in pediatric and adult patients. Spinraza is supplied as a solution to be administered intrathecally and treatment is initiated with 4 loading doses. The first 3 loading doses is administered at 14-day intervals and the 4th loading dose is administered 30 days after the 3rd dose. Maintenance doses are administered once every 4 months thereafter.

Zolgensma (onasemnogene abeparvovec; Formerly AVXS-101) is the first gene therapy for a neuromuscular disease and the first FDA-approved gene replacement therapy for SMA. Gene therapy uses a viral vector, non-replicating recombinant adeno-associated virus serotype 9 (AAV9) which crosses the blood-brain barrier, to

deliver a functional copy of the SMN1 gene and restore production of a working and full-length protein in motor nerve cells. Gene therapy offers the opportunity for single dose treatment of the disease and targets the root cause of SMA by delivering a fully functional SMN gene into target motor neuron cells. Zolgensma uses the viral vector, AAV9, to deliver the missing SMN gene and because AAV9 is a naturally occurring virus, some pediatric patients may have antibodies against this virus, causing these patients to be ineligible for treatment. It is reported that in 150+ patients treated with Zolgensma, only 5% of screened patients up to 5 years old excluded due to AAV9 antibody titers greater than 1:50 (Novartis 2019). The most common adverse reactions (incidence ≥ 5%) were elevated aminotransferases and vomiting. Adverse events also include thrombocytopenia, elevated blood creatine phosphokinase, elevated troponin, croup, lethargy, and hypercalcemia.

Zolgensma was approved by the FDA in 2019 for the treatment of children less than two years of age with SMA who have bi-allelic mutations in SMN1. The indication encompasses all SMA patients; however, there is limited published data and evidence of efficacy on older children, adults, SMA Type 0 and 4, and patients who already have advanced disease or ventilation needs. Patients less than 2 years of age was evaluated in an open-label, single-arm clinical trial (ongoing STR1VE trial; n=21) and an open-label, single-arm, ascending-dose clinical trial [completed START (Gene Transfer Clinical Trial for SMA Type 1; n=15) involving a total of 36 pediatric patients (AveXis 2019; Mendell 2017). The Biologics License Application (BLA) is supported by data from the START trial which evaluated Zolgensma in 15 patients with SMA type 1 (Mendell et al., 2017). Only symptomatic SMA type 1 patients with two copies of the SMN2 gene were enrolled in the completed Zolgensma trials. Clinical trials in patients with other forms of SMA, such as pre-symptomatic, SMA type 2, or SMA type 3 are ongoing. There is the potential for Zolgensma to provide benefit in pre-symptomatic SMA patients, yet there is currently no data to establish efficacy in this population.

Type 0 and 4. No clinical trials or evidence to support the safety and efficacy of Zolgensma in SMA Type 0 and 4 at this time.

Type 1 (Infantile-Onset). Zolgensma has been studied in 2 open-label clinical studies in symptomatic patients with SMA Type 1. Both clinical studies, STR1VE and START, have been completed. Children in both clinical studies had 2 copies of the SMN2 backup gene and experienced symptoms of SMA before 6 months of age (Novartis 2020).

- In the START [Gene Transfer Clinical Trial for SMA Type 1] trial, all 15 patients infused with Zolgensma were alive and without the need for permanent ventilation at 24 months. 92% (11/12) of patients who received the proposed therapeutic dose of Zolgensma could sit unassisted for ≥5 seconds, a milestone never achieved in the natural history of SMA Type 1. Natural history indicates that more than 90% of untreated patients with SMA Type 1 will die or require permanent ventilation by 24 months of age. Patients who voluntarily enrolled in an ongoing observational long-term follow-up of the START trial have maintained their developmental motor milestones, including patients who are four years post infusion, with some achieving additional motor milestones. The most common observed side effect in the Zolgensma clinical trial was elevated liver enzymes.

Type 2 and 3. Clinical evidence for Type 2 and 3 SMA are not available at this time. Clinical trials are currently recruiting.

Comparison to Spinraza. Key baseline characteristics of the two key trials (ENDEAR for Spinraza and CL-101 for Zolgensma). Infants in both trials had two copies of SMN2. Infants in the ENDEAR/Spinrza trial were diagnosed and treated later, on average, than those in CL-101/Zolgensma. Considering these differences, direct comparisons between the trials' results should not be made.

The best available published evidence to date on Zolgensma is from the START Trial. The efficacy of Zolgensma was evaluated in one open-label, single-arm clinical trial (ongoing STR1VE trial) and one open-label, single-arm, ascending dose clinical trial (completed; START). In both trials, Zolgensma was delivered as a single-dose intravenous infusion.

A number of pivotal studies defining the appropriate patient population for Zolgensma are currently ongoing and the patient selection criteria will be evaluated and revised as clinical trial results and evidence become available.

COVERAGE POLICY

Zolgensma (onasemnogene abeparvovec) gene therapy for the treatment of SMA **may be considered medically necessary** when **ALL** of 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; **AND**

2. Definitive diagnosis of SMA Type 1
   Informational Note: The best available evidence at this time is the published Phase I START trial (Mendell et al., 2017) open-label trial evaluating the safety and efficacy of Zolgensma in pediatric patients with SMA type 1 with homozygous SMN1 exon 7 deletions and 2 copies of SMN2. No data were available on Zolgensma in patients with Type 2 SMA and thus the evidence is insufficient at this time. (ICER Final Report, April 3, 2019; Updated May 24, 2019).

AND

3. Genetic testing/newborn screening confirms the presence of **ONE** of the following:
   a. Homozygous deletions of SMN1 gene (e.g., homozygous deletion of exon 7 at locus 5q13); **OR**
   b. Homozygous mutation in the SMN1 gene (e.g., biallelic mutations of exon 7); **OR**
   c. Compound heterozygous mutation in the SMN1 gene [e.g., deletion of SMN1 exon 7 (allele 1) and mutation of SMN1 (allele 2)]

   Informational Note: Genetic testing is the standard diagnostic test for SMA, which is supported by a consensus statement published in 2007 by The International Conference on the Standard of Care for SMA; in 2017, the group issued an update to the previous statement. In the new consensus statement, the group recommends genetic testing of SMN1 and SMN2 as the first line of examination when SMA is suspected. Testing of SMN2 should be conducted primarily to determine the severity of the condition.

AND

3. Two or fewer copies of SMN2 gene
   Informational Note: Disease severity in SMA generally correlates inversely with SMN2 gene copy number, which varies from 0 to 8 in the normal population (UTD) Only symptomatic SMA type 1 patients with two copies of the SMN2 gene were enrolled in the completed Zolgensma trials.

AND

4. Less than 6 months of age at the *onset of symptoms*. Documentation and medical records required; **AND** Less than 2 years of age at *administration* of Zolgensma.
   AND
   For premature neonates: Full-term gestational age must be reached. Documentation required.
   Informational Note: Delay Zolgensma infusion until full-term gestational age is reached. 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 (Novartis, 2019). The safety of Zolgensma was studied in pediatric patients who received Zolgensma infusion at age 0.3 to 7.9 months (weight range 3.0 kg to 8.4 kg). The efficacy of Zolgensma was studied in pediatric patients who received Zolgensma infusion at age 0.5 to 7.9 months (weight range 3.6 kg to 8.4 kg).

   Informational Note:
   - *Approval of gene therapy for SMA with Zolgensma is based on clinical trials with patients with SMA less than 6 months of age. START trial: 9 months of age or younger who developed symptoms of SMA prior to 6 months of age (Mendell et al., 2017). All 11 patients who achieved milestones were 6 months of age or less at the time of gene therapy administration (including sitting, talking and some patients walking). The one patient not experiencing advanced motor milestone achievement was 8 months of age at the time of gene therapy administration. STR1VE (Phase 3) trial: Less than 6 months of age (< 180 days) of age at the time of AVXS-101 infusion.*
   - *There are no completed studies on treatment with Zolgensma in patients ages 2 years and older at this time (November 2020). A Phase I clinical trial, STRONG (NCT03381729), is assessing the safety and tolerability of Zolgensma in 27 children, up to age 5. This study has completed enrollment. AveXis presented interim data from the STRONG clinical trial at the 2019 American Academy of Neurology (AAN) conference that is promising. The interim data showed motor function improvements in patients with SMA type 2 after a single intrathecal injection of Zolgensma. Results pending.*

AND

4. Member is less than 13.5 kg. Submit current weight (in kilograms) for determination of dosage.
   Informational Note: In the consideration of the currently available data and existing treatment alternatives, it is recommended that gene replacement therapy with Zolgensma for patients with a body weight >13.5 kg only be performed under a more rigorous protocol with continuous monitoring of safety and efficacy which might be best achieved in a clinical trial setting (Consensus statement 10: European ad-hoc consensus statement on gene replacement therapy for SMA).

AND

5. 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:
   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.

   AND

   b. Member has not previously received gene therapy, or Zolgensma;

   AND

   c. Member is not currently receiving therapy with an investigational or commercial product, including Spinraza (nusinersen) or Evrysdi (risdiplam), for the treatment of SMA
      NOTE: There are no data to render clinical judgments regarding the risks and benefits of adding Zolgensma treatment to ongoing treatment with Spinraza or Evrysdi; therefore, treatment must be discontinued prior to therapy with Zolgensma. For members who have not experienced sustained or substantial clinical benefit, or for members experiencing adverse events, submission of additional clinical information may be required. **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.

AND

7. 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
      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)
   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.

   Informational Note: When administered after the age of 6 months and/or in advanced stages of the disease, there are so far no published data on efficacy and safety (Consensus statement 10: European ad-hoc consensus statement on gene replacement therapy for SMA)

AND

8. Baseline (pre-treatment) laboratory tests within normal limits. Required within 30 days of request.
   a. Liver function: normal clinical exam, total bilirubin, and prothrombin time; AST and ALT levels <2 x Upper Limit of Normal

   AND

   b. Platelet count; **AND**
   c. Troponin-I.
      Informational Note: Transient increases in cardiac troponin-I levels (up to 0.176 µg/L) were observed following Zolgensma infusion in clinical trial. The clinical importance of these findings is not known; however, cardiac toxicity was observed in animal studies.

AND

9. Baseline anti-AAV9 antibody titers of no more than **less than or equal to** 1:50 prior to infusion, measured using an enzyme-linked immunosorbent assay (ELISA). Documentation required.
   Informational Note: The safety and efficacy of Zolgensma patients with anti-AAV9 antibody titers above 1:50 have not been evaluated. In Zolgensma clinical trials, patients were required to have baseline anti-AAV9 antibody titers of ≤ 1:50, measured using an ELISA (STR1VE, START).

AND

10. **Respiratory insufficiency:** 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[START]
    c. Use of non-invasive ventilation (BiPAP) beyond use for naps and nighttime sleep

    NOTE: There are no data on the use of Zolgensma among permanently ventilated patients; therefore, Zolgensma is considered investigational in patients who already require permanent ventilation due to the lack of evidence demonstrating safety and efficacy in those patients.

CONTINUATION OF THERAPY

Zolgensma is indicated to be dosed and infused one time only. Repeat treatment in individuals who have received Zolgensma previously is not supported by compendia and not considered not medically necessary. The safety and effectiveness of repeat administration of ZOLGENSMA have not been evaluated. (Prescribing Information, 2019)

The use of Zolgensma in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated. (Prescribing Information, 2019).

LIMITATIONS AND EXCLUSIONS

There are no contraindications listed in the manufacturer's labeling. The following are considered **exclusions** based on insufficient evidence:

1. Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
2. Concomitant use of any of the following: 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 within 3 months of planned Zolgensma therapy.
3. Concurrent therapy with an investigational or commercial product, including but not limited to: Spinraza (nusinersen), Evrysdi (risdiplam)
   NOTE: There are no data to render clinical judgments regarding the risks and benefits of adding Zolgensma treatment to ongoing treatment with Spinraza or Evrysdi; therefore, treatment must be discontinued prior to therapy with Zolgensma. For members who have not experienced sustained or substantial clinical benefit, or for members experiencing adverse events, submission of additional clinical information may be required. 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.
4. ANY of the following concomitant medical condition(s):
   a. Tracheostomy or current prophylactic use or requirement of noninvasive ventilatory support at any time and for any duration prior to screening or during the screening period.
   b. Hypoxemia (*oxygen saturation <96% awake or asleep without any supplemental oxygen or respiratory support*) at the screening visit or for altitudes >1000 m, oxygen saturation <92% awake or asleep without any supplemental oxygen or respiratory support at the screening visit.
   c. Signs of aspiration/inability to tolerate non-thickened liquids based on a formal swallowing test performed as part of screening or patients receiving any non-oral feeding method.
   d. Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening.
   e. Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner *within 4 weeks* prior to dosing.

f. Severe non-pulmonary/respiratory tract infection *within 4 weeks* before administration of gene replacement therapy or concomitant illness that, in the clinical judgment of the Prescriber, creates unnecessary risks for gene replacement therapy such as: Major renal or hepatic impairment; Known seizure disorder; Diabetes mellitus; Idiopathic hypocalciuria; Symptomatic cardiomyopathy.

5. 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
6. Clinically significant abnormalities in hematology or clinical chemistry parameters [i.e., GGT > 3X ULN, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.8 mg/dL, Hgb < 8 or > 18 g/Dl; WBC > 20,000 per cm]
7. Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus)

The following are considered **experimental, investigational and unproven** based on insufficient evidence:

1. Any indication other than those listed above
   Based on the peer-reviewed medical literature the safety and effectiveness for indications other than the medically necessary indication listed above has not been established.
2. Prior treatment, or being considered for treatment, with gene therapy, prior antisense oligonucleotide treatment, or cell transplantation for SMA
3. SMA Type 0 or 4: There is insufficient evidence to support safety and efficacy in SMA Type 0 or 4.
   SMA Type 4 is very rare. It usually surfaces in adulthood, and it leads to mild motor impairment. While symptoms can begin as early as age 18, they usually begin after age 35.
4. 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).
5. 2 years of age and older: Zolgensma is indicated for the treatment of pediatric patients under 2 years of age with SMA with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.
6. Permanent Ventilation: Permanently ventilated is 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, including: Invasive ventilation or tracheostomy; Pulse oximetry < 96% saturation; Use of non-invasive ventilation (BiPAP) beyond use for naps and nighttime sleep.)

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

QUANTITY LIMITATIONS: A one-time authorization of one dose (kit) of Zolgensma per lifetime; dosage is based upon documented weight (in kilograms). Please see the Zolgensma Treatment Guide for further dosing information. Additional infusions of will not be authorized.

ADMINISTRATION:

1. Administered as a single, one-time (slow IV infusion only; over 60 minutes) by healthcare professionals experienced in the diagnosis and management of SMA do not administer as IV push or bolus.
2. Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

DOSING CONSIDERATIONS: The intravenous dosage is determined by patient body weight, with a recommended dose of 1.1×10^{14} vector genomes (vg) per kg of body weight for pediatric patients and administered as an IV infusion over 60 minutes.

Concomitant therapy: Beginning the day prior to Zolgensma infusion, oral prednisolone (1 mg/kg/day or equivalent) should be administered and continued for at least 30 days to help prevent hepatic toxicity. At the end of 30 days, clinically assess liver and test hepatic function (ALT, AST, total bilirubin, and prothrombin time [PT]); if unremarkable findings (normal clinical exam, total bilirubin, and PT, and ALT and AST concentrations <2 x ULN), taper prednisolone over 28 days. If evidence of hepatic impairment exists, continue oral prednisolone (1 mg/kg/day or equivalent) until AST/ALT <2 x ULN and all other assessments return to normal, then taper over 28 days. If unresponsive to corticosteroid therapy, consult expert.

MONITORING PARAMETERS:

- Anti-AAV9 antibody testing at baseline (may re-test if anti-AAV9 antibody titers are reported >1:50)
- Liver function: Clinical exam, AST, ALT, total bilirubin, prothrombin time at baseline, weekly for the first month, then every other week for the second and third months; continue testing until results are unremarkable (normal clinical exam, total bilirubin and prothrombin time; AST and ALT levels <2 x ULN).
- Platelet count: Baseline, weekly for the first month, then every other week for the second and third months; continue testing until platelet count returns to baseline.
- Signs and symptoms of thrombotic microangiopathy (e.g., hypertension, bruising, decreased urine output, seizures).
- Troponin-I: Baseline, weekly for the first month, then monthly for the second and third months; continue testing until troponin-I level returns to baseline.

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.

DRUG INFORMATION

ROUTE OF ADMINISTRATION: Intravenous Infusion

DRUG CLASS: Gene Therapy, Adeno-Associated Virus

FDA-APPROVED USES:

SMA: 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 (FDA approved May 24, 2019)

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.

COMPENDIAL APPROVED OFF-LABELED USES: None

RISK EVALUATION AND MITIGATION STRATEGY (REMS): N/A

BOXED WARNING: Acute serious liver injury
Acute serious liver injury and elevated aminotransferases can occur with Zolgensma. Patients with preexisting liver impairment may be at higher risk. Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing [e.g., hepatic aminotransferases (AST and 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.

Warnings/Precautions

- 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.
- 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.

SUMMARY OF MEDICAL EVIDENCE

Clinical Trials for Zolgensma

PHASE	DESCRIPTION	SMA TYPE	STATUS
Phase 1	**START:** Gene Transfer Clinical Trial for SMA Type 1 NCT02122952	Type 1	Completed Published
	Long-Term Follow-up to the START trial NCT03421977	Type 1	**Active,** not recruiting
Phase 3	**STR1VE:** Gene Replacement Therapy Clinical Trial for Patients with SMA Type 1 NCT03306277	Type 1	Completed Nov 12, 2019
Phase 3	**STR1VE-EU** Single-Dose Gene Replacement Therapy Clinical Trial for Patients with SMA Type 1 NCT03461289	Type 1	Completed Sep 11, 2020
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	Completed July 15, 2021
Phase 1	**STRONG:** Study of Intrathecal Administration of AVXS-101 for SMA NCT03381729	Type 2 Type 3 (up to 60 months old)	Suspended (as of Nov 2020). Last update posted June 9, 2021

At this time, pivotal studies defining an appropriate patient population for this drug are ongoing, therefore the patient selection criteria will be evaluated and revised as clinical trial results and evidence are published.

Type 1 SMA

The efficacy of Zolgensma was evaluated in an open-label, single-arm clinical trial (STR1VE trial) and one open-label, single-arm, ascending dose clinical trial (START). In both trials, Zolgensma was delivered as a single-dose IV infusion.

- Phase 1 open label trial evaluating the safety and efficacy of Zolgensma in pediatric patients with SMA type 1 with homozygous *SMN1* exon 7 deletions and 2 copies of *SMN2*
- Participants of this trial were assigned to receive 1) a single IV infusion of low-dose Zolgensma at 6.7 x 10^{13} vector genomes per kilogram (vg/kg) (n=3), or 2) high-dose Zolgensma at 2.0 x 10^{14} vg/kg (n=12)
- Oral prednisolone was given to 14 of 15 participants on the day prior to infusion, and then administered daily for approximately 30 days after infusion. Patients returned for follow up visits on days 7, 14, and 30, followed by monthly visits for up to 2 years post-infusion.
- Mean age: 6.3 months in the low-dose cohort and 3.4 months in the high-dose cohort. At baseline, all of the patients in the low-dose cohort required both nutritional and ventilatory support, whereas 42% of patients in the high-dose cohort required nutritional support and 17% required ventilatory support.
- Primary outcome was treatment-related adverse events (AEs) of grade 3 or higher
- The secondary outcome was the time until death or the need for permanent ventilation support, defined as at least 16 hours per day of continuous ventilation for at least 14 days (excluding ventilatory assistance for acute, reversible illness or a perioperative state).
- Exploratory analyses included a comparison of scores on the CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) scale of motor function (ranging from 0 to 64, with higher scores indicating better function) in the 2 cohorts and motor milestones in the high-dose cohort with scores in studies of the natural history of the disease (historical cohorts).
  - Serious AEs occurred in 86.7% of all patients. Of these serious AEs, 2 cases of elevated serum aminotransferase levels without clinical sequelae (1 from each cohort) were deemed as grade 4 treatment-related AEs. Three non-serious AEs were deemed treatment-related AEs, consisting of asymptomatic elevations in serum aminotransferase levels. All patients were alive, and none of the

patients required permanent mechanical ventilation at 20 months of age. In contrast, only 8% of the patients in a historical cohort did not require permanent mechanical ventilation.

- At baseline, the mean CHOP INTEND score for the low-dose cohort and the high-dose cohort were 16 and 28, respectively.
- Results: Improvements from baseline were observed in both cohorts, with a mean increase of 7.7 points in the low-dose cohort and a mean increase of 24.6 points in the high-dose cohort, compared with a decline in this score in the historical cohort.
- Of the 12 patients in the high-dose cohort, 11 patients were able to sit unsupported for at least 5 seconds, 11 patients were able to control head movements, 9 patients were able to roll, and 2 patients were able to crawl, stand unassisted, and walk independently.
- A report on health outcomes in patients enrolled in the high-dose cohort of the START trial is also available (Al Zaidy et al., 2018).

Al-Zaidy et al. (2019) reported on additional health outcomes in patients enrolled in the high-dose cohort of the START trial (n=12) for 24 months

- The investigators reported on pulmonary ventilation support, nutritional support, swallow function, and hospitalization rate. The assessment of pulmonary support consisted of the number of hours per day the patient required ventilation support over the 2 weeks prior to the study visit. Nutritional support and swallow function were determined by video-fluoroscopic swallow studies. Planned and unplanned hospitalizations were calculated for each patient; the annualized hospital rate was calculated as the number of hospitalizations divided by the total number of study days.
- Non-invasive ventilation (NIV) was required for 2 patients prior to gene replacement therapy, and 3 additional patients required NIV by the final study visit. By the end of the study, 11 of 12 patients were able to safely swallow to allow for at least partial oral feeding, and 6 patients were exclusively eating by mouth. The vast majority of the patients (83%) had at least 1 hospitalization. The mean unadjusted annualized hospitalization rate was 2.1, and the mean length of stay per hospitalization was 6.7 days.

***STR1VE*:** Gene Replacement Therapy Clinical Trial for Patients with SMA Type 1 (Phase 3, single-arm trial; infants)
STR1VE is a global Phase 3 clinical program that includes open-label, single-arm, single-dose, multi-center trials (STR1VE-US in the United States, STR1VE-EU in Europe and STR1VE-AP in Asia Pacific) designed to evaluate the efficacy and safety of a single, one-time IV infusion of Zolgensma in symptomatic patients with SMA Type 1 who are less than 6 months of age at the time of gene therapy, with 1 or 2 copies of the SMN2 backup gene and who have bi-allelic SMN1 gene deletion or point mutations.

Enrollment in the study is complete with 22 patients with 2 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).

STR1VE-US: Study Completed
STR1VE-US is a part of the global Phase 3 STR1VE clinical program.

- STR1VE-US is the first trial in symptomatic patients with SMA Type 1 to incorporate the stringent composite endpoint of 'ability to thrive.'
- 20 of 22 patients (91%) met the co-primary efficacy endpoint of event-free survival at 14 months, and 13 of 22 patients (59%) met the co-primary efficacy endpoint of functional sitting for ≥30 seconds at 18 months of age. 13 patients (59.1%) achieved the developmental milestone of functional independent sitting for ≥30 seconds (P<0.0001 vs natural history) at the 18 months of age study visit. A 14th patient achieved the milestone of sitting independently for 30 seconds at 16 months of age, but this milestone was not confirmed at the month 18 visit. 15 patients (68.2%) did not require non-invasive ventilatory support at any point during the study. 18 of 22 patients (81.8%) did not use ventilatory support (as assessed by Trilogy BiPAP data) at 18 months of age.
- Of the 22 patients, 9 (40.9%) achieved this co-secondary endpoint at 18 months of age (P<0.0001 vs natural history), including 19 patients (86.4%) who did not receive nutrition through any feeding tube or other non-

oral method, 14 patients (63.6%) who maintained weight (greater than third percentile) consistent with gender and age and 12 patients (54.5%) who were able to tolerate thin liquid.

- Patients achieved rapid and sustained improvement in motor function unseen in natural history. The average increase in CHOP-INTEND scores were 6.9 points at 1 month (N=22), 11.7 points at 3 months (N=22) and 14.6 points at 6 months (N=20) after gene therapy treatment. 21 of 22 patients (95%) achieved a CHOP INTEND score of 40 or greater, and 14 (63.6%) achieved a CHOP INTEND score 50 or greater.
- 11 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.
- Day et al. (2021) reported on the results of this multicenter trial which build on findings from the phase 1 START study by showing safety and efficacy of commercial grade onasemnogene abeparvovec. Onasemnogene abeparvovec demonstrated statistical superiority and clinically meaningful responses when compared with observations from the Pediatric Neuromuscular Clinical Research (PNCR) natural history cohort. The favorable benefit-risk profile of onasemnogene abeparvovec supports its use for treatment of symptomatic patients with genetic or clinical characteristics predictive of infantile-onset SMA type 1.

STR1VE-EU: Phase 3, single-arm trial of infants with Type 1 SMA

- STR1VE-EU is a single-arm phase 3 trial done at 9 sites in Italy, the United Kingdom, Belgium, and France. Patients younger than 6 months with SMA Type 1 with the SMN1 exon 7–8 deletion or point mutations, and one or two copies of SMN2. 32 of 33 patients completed the study.
- Results from the phase 3 STR1VE-EU confirmed the safety and efficacy findings of the phase 1 START and phase 3 STR1VE-US studies. The STR1VE-EU trial demonstrated rapid improvements in motor function following treatment with Zolgensma, and most patients achieved motor milestones not observed in the natural history of SMA Type 1.
- Mercuri et al. 2021 reported that they 14 of the 32 patients achieved the primary end point of functional independent sitting for at least 10 seconds at any visit up to the 18 months of age, which is a WHO developmental milestone of independent sitting. None of the 23 patients in a matched, untreated natural history cohort achieved this end point. Additionally, 31 of 32 of the patients who received Zolgensma survived free from permanent ventilatory support at 14 months.
- Safety remained consistent with previously reported data though further studies are required to show long-term safety (Mercuri et al. 2021). The benefit-risk profile of Zolgensma seems promising for this patient population, including those with severe disease at baseline.

Pre-Symptomatic Patients Likely to Develop Type 1 SMA

SPR1NT: Pre-Symptomatic Study of Intravenous AVXS-101 in SMA for Patients with Multiple Copies of SMN2
Phase 3, open-label, single-arm, multi-center trial designed to evaluate the safety and efficacy of a one-time IV infusion of Zolgensma in pre-symptomatic patients with a genetic diagnosis of **SMA and 2 or 3 copies** of SMN2 who were ≤6 weeks of age.

- Data reported reflect the final data cut for SPR1NT two-copy patients. Mean age at dosing in the two-copy cohort was 20.6 days (8-34 days). The study of the three-copy cohort is ongoing. Two-copy cohort (n=14) results:
- 100% of patients (14/14) met the secondary endpoint of survival without ventilatory support of any kind at 14 months of age, versus only 26 percent of patients in the PNCR natural history cohort.
- All patients (100%) achieved the primary endpoint of sitting independently for at least 30 seconds, including 11 (79%) who achieved this milestone within the WHO window of normal development.
- 11 patients (79%) could stand independently, seven of whom achieved this milestone within the WHO window of normal development.
- 9 patients (64%) could walk independently, five of whom achieved this milestone within the WHO window of normal development.
- All patients (100%) were independent of nutritional and respiratory support for the duration of the study.
- Nearly all patients (13/14) achieved the additional secondary efficacy endpoint of age-appropriate weight maintenance without non-oral feeding support at any visit up to 18 months of age.

- All patients (100%) achieved or maintained a CHOP INTEND score of ≥ 58. According to natural history, untreated patients with SMA Type 1 almost never achieve a CHOP INTEND score of ≥ 40.
- All patients (100%) had Bayley-III fine motor performance scores like same-age peers without SMA and the majority (64%) had gross motor performance scores like same-age peers without SMA.

Summary: SPR1NT clinical trial demonstrate age-appropriate milestone development in pre-symptomatic children with SMA without respiratory or nutritional support of any kind, and with no serious, treatment-related adverse events. All children (100%) treated pre-symptomatically in the SPR1NT two-copy cohort achieved event-free survival, were independent of respiratory and nutritional support and met the primary endpoint of sitting independently for ≥ 30 seconds, including 11/14 (79%) who achieved this milestone within the WHO window of normal development. Most patients went on to stand independently (11/14) and walk independently (9/14), most within the typical range of normal development.

Type 2 SMA

STRONG: Study of Intrathecal Administration of AVXS-101 for SMA
Phase 1, open-label, dose-comparison, multi-center trial designed to evaluate the safety and tolerability of one-time intrathecal administration of Zolgensma in patients with SMA Type 2 who have 3 copies of the SMN2 gene, and who are able to sit but cannot stand or walk at the time of study entry. Patients were stratified into two groups based on age at time of dosing. Three dosing strengths are being evaluated.

- Patients were stratified into two groups based on age at time of dosing: patients who are ≥ 6 months but < 24 months, and patients who are ≥ 24 months but < 60 months. The primary efficacy outcome for patients in the first group is the ability to stand without support ≥ 3 seconds; the main goal for the second group is a change in Hammersmith Functional Motor Scale-Expanded (HFMSE) score from baseline. Since dosing, 22 motor milestones in 10 patients have been achieved across Dose A and Dose B, including two patients who gained the ability to stand independently, one of whom went on to walk alone, and one patient who gained the ability to walk with assistance. The median duration of follow-up was 6.5 months.
- In this Phase I dose comparison trial (STRONG) of intrathecal administration of Zolgensma in patients with Type 2 SMA, treatment was well tolerated with two serious adverse events of transaminase elevation. A number of the patients achieved new motor milestones.
- All patients (n=30) were alive. There were two serious treatment-related adverse events. Both were of transaminase elevation. The frequency of patients with adverse events of transaminase elevation appeared to be lower than that seen with IV administration of Zolgensma.
- As of March 2019, 30 patients have been enrolled and received intrathecal Zolgensma. Interim data from this multicenter study showed improvements in motor function in patients with type 2 SMA.
- On October 30, 2019, the FDA placed partial hold on clinical trials for intrathecal administration of Zolgensma 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 IV Zolgensma clinical trials. The clinical hold pends further discussions regarding pre-clinical findings.

HAYES. According to a comprehensive assessment, 'Onasemnogene Abeparvovec-xioi (Zolgensma) for Spinal Muscular Atrophy', a very-low-quality body of evidence does not allow for conclusions to be drawn regarding the efficacy or safety of onasemnogene abeparvovec in infants with SMA type 1. The report notes that substantial uncertainty exists due to the very small body of published evidence and the lack of directly comparative studies with statistical analyses. Hayes assigned a rating to reflect this very-low-quality body of evidence derived from one small single-arm study in the use of onasemnogene abeparvovec in infants with SMA type 1, confirmed bi-allelic deletions of SMN1, and 2 copies of SMN2. A poor rating was also assigned for use of onasemnogene abeparvovec in individuals with other types of SMA, or with > 2 copies of SMN2 due to the lack of evidence for the use of onasemnogene abeparvovec in these populations. The report also indicates that there is insufficient evidence to establish definitive patient selection criteria for onasemnogene abeparvovec treatment.

National and Specialty Organizations

American Academy of Neurology (AAN). At the 2019 AAN conference, interim data from the STRONG, SPR1NT, and STR1VE clinical trials. Results from multiple trials of *SMN1*gene-replacement therapy showed promise for single-dose treatment of SMA.

- The Phase 1 STRONG study showed motor function improvements in patients with SMA type 2 after a single *intrathecal i*njection of Zolgensma.
- In the SPR1NT trial, SMA patients with 2 or 3 copies of the *SMN2* gene, who were pre-symptomatic, showed increased motor function and milestone achievements.
- The STR1VE trial continued to show improved results in CHOP-INTEND scores, and 13 of the 15 infants had reached 13.6 months of age without the need for permanent ventilation.

SMA Newborn Screening Multidisciplinary Working Group
A working group comprised of 15 SMA experts of clinicians and geneticists convened to develop treatment guidelines for infants who test positive during the newborn screening process (Glascock 2018). The guidelines are based on the knowledge that disease severity is directly correlated with the underlying genetic alteration that promotes SMA.
NOTE: This treatment algorithm was published prior to the approval of Zolgensma.

- The recommendation is that all infants with confirmed SMA type 1 or 2 (the most common and severe forms of the disease) who have only 2 or 3 copies of the *SMN2* gene should receive immediate treatment with an *SMN* up-regulating therapy (n=13). For those infants in which immediate treatment is not recommended, guidelines were developed that outline the timing and appropriate screens and tests to be used to determine the timing of treatment initiation.
- All infants with confirmed SMA type 1 or 2 (the most common and severe forms of the disease) who have only two or three copies of the *SMN2* gene should receive immediate treatment with an *SMN* up-regulating therapy.
- SMA Types 2 or 3 with 3 or fewer copies of the *SMN2* treatment with a disease modifying gene: immediate treatment with a disease modifying therapy and referral to both a neuromuscular specialist and a geneticist is recommended; for those with only one copy of *SMN2* who are symptomatic at birth, the attending physician should determine whether the patient and family would benefit from treatment.
- Patients with four copies of *SMN2* should be screened periodically for symptoms and referred to a geneticist to determine the exact number of *SMN2* copies, however immediate therapy is not recommended.
- For those infants in which immediate treatment is not recommended, guidelines were developed that outline the timing and appropriate screens and tests to be used to determine the timing of treatment initiation.

In 2020, the Working Group updated recommendations that infants diagnosed with SMA via newborn screening with 4 SMN2 gene copies should receive immediate treatment. Also, patients with 5 (or more) SMN2 gene copies should be observed and screened for symptoms (Glascock 2020). The working group acknowledged that current laboratory assays designed to detect SMN2 copy number often have difficulty distinguishing high copy numbers of SMN2 and that many laboratories report results as 4 or more SMN2 copies, being unable to provide an exact number. As a result, follow-up with a laboratory able to distinguish exact SMN2 copy number is recommended.

2020 European Neuromuscular Expert Ad-Hoc Consensus Statement on Gene Replacement Therapy for SMA (Kirschner J, 2020)
11 consensus statements covering qualification, patient selection, safety considerations and long-term monitoring were presented by a group of 13 European neuromuscular experts after the European Medical Agency (EMA) approval of Zolgensma in May 2020. The following recommendations were considered ‘strong’ statements and received 100% consensus 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 pre-symptomatic 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 pre-symptomatic 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: Approval of gene therapy for SMA with Zolgensma is based on clinical trials with patients with SMA less than 6 months of age. Additional data of patients up to 2 years and weighing up to 13.5 kg are made public through congress presentations. These data mainly come from non-systematic data collection in the US, where Zolgensma is approved up to the age of 2 years. When administered after the age of 6 months and/or in advanced stages of the disease, parents or patients should clearly be made aware that there are so far no published data on efficacy and safety. In this patient population it is particularly important for physicians to discuss the benefit/risk ratio 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 directly proportional with the weight, patients above 13.5 kg should only be treated in specific circumstances. For these patients, treatment with other disease modifying therapies or future intrathecal administration of Zolgensma should be considered as an alternative.
- Consensus statement 6: Until now there is no published evidence that combination of two disease modifying therapies (e.g., gene therapy and nusinersen) is superior to any single treatment alone.
- 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 treatment-- ideally in the pre-symptomatic stage of the disease – is associated with markedly better outcome as compared to later start of treatment. SMA is therefore a good candidate for inclusion in newborn screening programs. In newly diagnosed patients any delay of treatment should be avoided. Ideally, the time frame between diagnosis and initiation of a disease modifying treatment should be no longer than 14 days. This is particularly important in infants due to the progressive course of the disease.
- 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: On the basis of the currently available data and in light of existing effective treatment alternatives, intravenous gene replacement therapy with Zolgensma for patients with a body weight >13.5 kg should only be performed under a more rigorous protocol with continuous monitoring of safety and efficacy. This data collection might be best achieved in a clinical trial setting.
- 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.

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". The recommendations above were presented with 100% consensus from the European expert panel.

SUPPLEMENTAL INFORMATION

Clinical Classification of SMA. Disease phenotypes are classified according to a scheme developed at the 1991 International Consortium on SMA sponsored by the Muscular Dystrophy Association; these phenotypes were modified into five subtypes on the basis of age of onset, inheritance pattern, and maximum motor function achieved (Kolb, 2015; Munsat, 1991).

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

Reference: Adapted from Table 1 of Verhaart et al. 2017; Number of SMN2 copies based on Calucho et al. 2018.
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.
Calucho M, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord. 2018;28(3):208-215.
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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.) Onset occurs before 6 months of age in about 60% of affected individuals; these patients usually do not live past 2 years old (Ross et al.).

Assessment Tools for Motor Development

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
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
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

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CODING & BILLING INFORMATION

CPT	Description
96365-96368	Intravenous (IV) infusion administration for therapy, prophylaxis, or diagnosis; initial, up to one hour

HCPCS	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

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APPROVAL HISTORY

Dec 8 2021	Policy reviewed and updated, no changes in coverage criteria, updated references. Notable content updates include Clinical Trials results.
Sep 2021	Policy converted to new template.
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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- Spinal muscular atrophy. Topic last updated: Aug 06, 2021. Topic 6146 Version 42.0.
- Overview of gene therapy, gene editing, and gene silencing. topic last updated: Aug 18, 2021. Topic 98724 Version 31.0.

APPENDIX

Reserved for State specific information *(to be provided by the individual States, not Corporate). Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

Centers for Medicare & Medicaid Services (CMS)

On August 7th, 2019 CMS published a National Coverage Determination (NCD) regarding CAR-T therapy coverage in the Medicare program. According to the NCD, for services performed on or after August 7, 2019, CMS covers autologous treatment for cancer with T-cells expressing at least one chimeric antigen receptor (CAR) when administered at healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies (REMS) and used for a medically accepted indication as defined at Social Security Act section 1861(t)(2) -i.e., is used for either an FDA-approved indication (according to the FDA-approved label for that product), or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia. Reference Publication 100-03, National Coverage Determination (NCD) **Manual Section 110.24** for complete coverage criteria. (Rev. 10454, Issued: 11-13-20, Effective: 08-07-19, Implementation: 02-16-21)

NOTE: On 11/2020, a Change Request (CR) was issued to inform of coverage effective for claims with dates of service on or after August 7, 2019 [Link: TN 10454 (Medicare Claims Processing)]