Subject: ZOLGENSMA (onasemnogene abeparvovec)	**Original Effective Date:** 6/18/2019
Policy Number: MCP-348	**Revision Date(s):**
Review Date(s): Q4 2020, 1/19/21	
P&T Approval Date:	

Contents

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. 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 (i.e., 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 document and provide the directive for all Medicare members.

RECOMMENDATION

This policy addresses ZOLGENSMA (onasemnogene abeparvovec) gene therapy for the treatment of **spinal muscular atrophy (SMA)**. The intent of this MCP is to ensure appropriate selection of patients for therapy based on available relevant evidence, product labeling, clinical guidelines, and clinical studies.

Molina Healthcare reserves the right to update this Policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

SUMMARY

SPINAL MUSCULAR ATROPHY (SMA)

- 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)
- 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)
- 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 in **APPENDIX 1: Clinical Classification of SMA**
- Life expectancy is inversely related with the age of onset, with higher mortality rates associated with early disease onset.
- Affects 1 per 8,000 to 10,000 people worldwide (Genetics Home Reference, 2019)
- 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
- The focus of treatment, prior to the approval of disease modifying therapies, has been on supportive care, symptomatic and related clinical problems that develop with age including, respiratory, nutritional, and orthopedic management:
    - 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
    - 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

The first disease modifying treatment of SMA was approved by the FDA in 2016 (Spinraza)

Spinraza (nusinersen)

- The first FDA-approved therapy for SMA
- Indicated for the treatment of SMA (any subtype) in pediatric and adult patients
- An antisense oligonucleotide, targets the messenger RNA from SMN2 so that it creates more functional SMN protein
- Administered via intrathecal injection (i.e., into the cerebrospinal fluid that surrounds the spinal cord and brain) with four loading doses (day 0, day 14, day 28, and day 63) and every four months thereafter

ZOLGENSMA (onasemnogene abeparvovec; Formerly AVXS-101)

- 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
  - Targets the root cause of SMA by delivering a fully functional SMN gene into target motor neuron cells
- Uses the AAV9 to deliver the missing SMN gene and because AAV9 is a naturally occurring virus, some pediatric patients may have antibodies against this virus, making them ineligible for treatment.
  - Over 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.
  - In **STR1VE** [Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1], 1 participant died of respiratory failure that was classified as unrelated to treatment after having had gains in motor milestone development.
  - A single enrollee in the **SPRINT** [Pre-Symptomatic Study of Intravenous AVXS-101 in Spinal Muscular Atrophy (SMA) for Patients with Multiple Copies of SMN2] was found to have 4 copies of SMN2, and thus included only in the safety and not efficacy analysis.

CLINICAL EVIDENCE

The FDA approved indication is for 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. The FDA approval of onasemnogene in pediatric 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 Spinal Muscular Atrophy Type 1) trial]; 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 (onasemnogene abeparvovec) in SMA Type 0 and 4. Therefore the evidence is insufficient evidence to support safety and efficacy of ZOLGENSMA in Type 0 or 4 SMA patients 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 Spinal Muscular Atrophy Type 1] trial, all 15 patients infused with ZOLGENSMA were alive and without the need for permanent ventilation at 24 months. Ninety-two percent (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 percent 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. Note that infants in ENDEAR were diagnosed and treated later, on average, than those in CL-101. Given 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.

At this time, a number of 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 become available.
Refer to 'Ongoing Trials' discussion in the Summary of Clinical Evidence' section of the policy.

FDA INDICATIONS

FDA-approved indication does not, alone dictate coverage. This coverage policy may not recommend coverage for all FDA-approved indications. Please review the policy in its entirety for indications covered by Molina Healthcare.

Spinal Muscular Atrophy: For the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene

Limitations of Use:

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

Available as: 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*

FDA Approved: May 24, 2019. *The FDA granted this application fast track, breakthrough therapy, priority review, and orphan drug designations.*

Black Box Warnings: Acute Serious Liver Injury and elevated aminotransferases can occur with onasemnogene abeparvovec. Patients with pre-existing 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 [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Administer systemic corticosteroid to all patients before and after onasemnogene abeparvovec infusion. Continue to monitor liver function for at least 3 months after infusion.

REMS: None at the time of this writing

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.

CLASSIFICATION: SMN Gene Therapy; AAV9 gene therapy vector

RECOMMENDATIONS/COVERAGE CRITERIA

ZOLGENSMA (onasemnogene abeparvovec) may be authorized for initial therapy for members who meet **ALL** the following criteria with clinical documentation **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed by, or in consultation with, a board-certified pediatric neurologist, neuromuscular specialist or neurologist with experience in the diagnosis and management of spinal muscular atrophy (SMA)

2. Diagnosis/Indication [ALL]

Documentation of diagnosis required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis. Submit all relevant clinical documentation at the time of the request.

- ❒ Clinical diagnosis of **SMA Type 1**
  - *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

❒ Genetic testing/newborn screening confirms the presence of ONE (1) of the following: [ONE]

- ❍ Homozygous deletions of SMN1 gene (e.g., homozygous deletion of exon 7 at locus 5q13)
- ❍ Homozygous mutation in the SMN1 gene (e.g., biallelic mutations of exon 7)
- ❍ Compound heterozygous mutation in the SMN1 gene [e.g., deletion of SMN1 exon 7 (allele 1) and mutation of SMN1 (allele 2)]

◆ *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

❒ Two or fewer copies of SMN2 gene

◆ *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.*

3. Age/Gender/Restrictions [ALL]

❒ Member is **less than 6 months of age** at the onset of symptoms. Documentation and medical records required.

◆ *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*

AND

❒ Less than 2 years of age at administration of Zolgensma

◆ *There are no completed studies on treatment with Zolgensma in patients ages 2 years and older at this time (November 2020).*

◆ *There is currently a Phase I clinical trial STRONG (NCT03381729), which will assess 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

❒ For premature neonates: Full-term gestational age must be reached. Confirmation/documentation required.

◆ *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)*

AND

❒ Member is less than 13.5 kg

- *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 spinal muscular atrophy)*

AND

❒ Prescriber confirm member's current and previous enrollment in clinical trials, any history of gene therapy, OR prior antisense oligonucleotide treatment, or cell transplantation related to SMA or ZOLGENSMA [ALL]

❍ Member is not currently enrolled in SMA clinical trials and is ineligible for clinical trial enrollment. NOTE: Members eligible for clinical trial enrollment may not be authorized.

AND

❍ Member has not previously received gene therapy, or ZOLGENSMA (onasemnogene abeparvovec) therapy

AND

❍ Member is not receiving therapy with an investigational or commercial product, including **Spinraza (nusinersen) or Evrysdi (risdiplam)** for the treatment of SMA

NOTE: Requests will **not** be authorized for members currently enrolled in SMA clinical trials, or who have previously received ZOLGENSMA. Individual should receive treatment and monitoring per clinical trial protocols in place by the applicable Institutional Review Board.

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. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ❒ Baseline motor function assessment using at least **ONE (1)** 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) [ONE]
  - ❍ †CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
    - *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)*
  - ❍ †HFMS: Hammersmith Functional Motor Scale
  - ❍ †HFMSE: Hammersmith Functional Motor Scale Expanded
  - ❍ Hammersmith Infant Neurologic Exam Part 2 (HINE-2)
  - ❍ 6-minute walk test (6MWT)
  - ❍ Upper Limb Module (ULM) score *(Non-ambulatory patients)*

  †Measures that have been developed and validated specifically for SMA populations

  MOLINA REVIEWER: Refer to APPENDIX 2 for additional information on 'Assessment Tools for Motor Development'

  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 spinal muscular atrophy)

AND

- ❒ Baseline (pre-treatment) laboratory tests *within 30 days of request*: [ALL]
  - ❍ Liver function: clinical exam, AST, ALT, total bilirubin, prothrombin time
  - ❍ Platelet count
  - ❍ Troponin-I
    - *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

- ❒ Baseline anti-AAV9 antibody titers of less than or equal to 1:50 prior to infusion, measured using an enzyme-linked immunosorbent assay (ELISA). Documentation required.
  - *In ZOLGENSMA clinical trials, patients were required to have baseline anti-AAV9 antibody titers of ≤ 1:50, measured using an ELISA (STR1VE, START). The safety and efficacy of ZOLGENSMA in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated*

- ❒ **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
  - ❍ Invasive ventilatory support
  - ❍ Pulse oximetry < 95% saturation[START]
  - ❍ 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.

5. Contraindications*/Exclusions/Discontinuations

Contraindications*/Exclusions/Discontinuations* *There are no contraindications listed in the manufacturer's labeling at this time.*

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications

- ❒ Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients

- ❒ Concomitant use of ANY of the following: [ANY]
  - ❍ Drugs for the treatment of myopathy or neuropathy OR diabetes mellitus
  - ❍ Plasmapheresis
  - ❍ Immunomodulators (i.e. adalimumab)
  - ❍ Immunosuppressive therapy within 3 months of ZOLGENSMA treatment (e.g. corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, intravenous immunoglobulin, rituximab)

- ❒ 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.

- ❒ Any history of gene therapy, prior antisense oligonucleotide treatment, or cell transplantation

- ❒ ANY of the following medical condition(s): [ANY]
  - ❍ 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
  - ❍ 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

- ❍ 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
- ❍ Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening
- ❍ Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 Weeks prior to dosing
- ❍ Severe non-pulmonary/respiratory tract infection *within 4 weeks* before administration of gene replacement therapy or concomitant illness that, in the opinion 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

❒ 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

❒ 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]

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

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

ZOLGENSMA (onasemnogene abeparvovec) is indicated to be dosed and infused one time only. Repeat treatment in individuals who have received ZOLGENSMA (onasemnogene abeparvovec) 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).

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. **Recommended Dosage**
   - ❒ 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
     - *Administered as an intravenous infusion over 60 minutes*
     - *Premedication (younger than 2 years): Initiate systemic corticosteroids equivalent to oral prednisolone 1 milligram per kilogram of body weight per day (1 mg/kg/day) for a total of 30 days*

2. **Authorization Limit [ALL]**
   - ❒ Quantity limit: Single, one-time infusion per lifetime. Additional infusions of onasemnogene abeparvovec (Zolgensma) will not be authorized.
   - ❒ Duration authorization: Infusion may be performed up to one (1) month from time of authorization OR until 2 years of age, whichever occurs first

3. **Route of Administration [ALL]**
   - ❒ Administered as a **single, one-time infusion** by healthcare professionals experienced in the diagnosis and management of SMA

COVERAGE EXCLUSIONS

This policy addresses ZOLGENSMA (onasemnogene abeparvovec) for the treatment of **spinal muscular atrophy (SMA)**.

All other uses of ZOLGENSMA (onasemnogene abeparvovec) that are not an FDA-approved indication AND not included in the 'Coverage Criteria' section of this policy is considered not medically necessary. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

- ❒ **SMA Type 0 or 4:** There is insufficient evidence to support safety and efficacy of nusinersen in SMA Type 0 or 4
  - SMA type IV 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.
- ❒ **2 years of age and older:** Indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene

- ❒ **Permanent Ventilation:** 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.**
  *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.

SUMMARY OF CLINICAL EVIDENCE

CLINICAL TRIALS FOR ZOLGENSMA			
PHASE	**DESCRIPTION**	**SMA TYPE**	**STATUS**
Phase I	Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1 (START) NCT02122952	SMA type 1	Completed Published
	Long-Term Follow-up to the START trial NCT03421977	SMA type 1	Active, not recruiting
Phase III	Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 (STR1VE) NCT03306277	SMA type 1	Completed November 12, 2019
Phase I	Study of Intrathecal Administration of AVXS-101 for Spinal Muscular Atrophy (STRONG) NCT03381729	SMA type 2 SMA type 3 (up to 60 months old)	Suspended (as of Nov 2020); Last update posted August 5, 2020
Phase III	Single-Dose Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1 (STR1VE-EU) NCT03461289	SMA type 1	Primary Completion September 11, 2020
Phase III	Pre-Symptomatic Study of Intravenous AVXS-101 in Spinal Muscular Atrophy (SMA) for Patients With Multiple Copies of SMN2 (SPR1NT) NCT03505099	SMA type 1 SMA type 2 SMA type 3	Active, not recruiting

CLINICAL TRIALS

STR1VE Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1
Phase 3, single-arm trial of infants with **Type 1 SMA** for treatment of SMA

- Genetically diagnosed (biallelic SMN1 mutations/deletions, 2 SMN2 copies), defined by nonfunctional SMN1 gene with 1 or 2 copies of survival motor neuron 2 gene (SMN2)
- 15 patients under 6 months (< 180 days) of age at the time of gene replacement therapy (Day 1) enrolled
- Of the 15 babies treated more than 13.6 months or who discontinued the study before then, 13 (87%) survived without needing permanent ventilation, in contrast to the 25-50% survival rate for children with SMA when untreated
- Of those who reached age 10.5 months or discontinued the study before then, 95% (19/20) survived without ventilation
- 11 can sit without support for at least 30 seconds, a milestone achieved at average age 11.9 months (mean 8.2 months post-treatment)
- **21 of 22 infants were alive with a median age of 14.4 months (the death was deemed not related to treatment)**
- **5 months after treatment, CHOP-INTEND scores increased by an average of 14.3 points, which was similar to the results from the START trial**
- CHOP-INTEND scores increased by an average of 6.9 points one month, 11.7 points three months and 14.3 points five months after gene transfer, reflecting improvement in motor function from baseline [achieved CHOP-INTEND score of ≥ 40]

STR1VE-US – Study Complete

- In STR1VE-US, 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. Thirteen 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. Fifteen patients (68.2%) did not require non-invasive ventilatory support at any point during the study. Eighteen of 22 patients (81.8%) did not use ventilatory support (as assessed by Trilogy BiPAP data) at 18 months of age.
- STR1VE-US is the first trial in symptomatic patients with SMA Type 1 to incorporate the stringent composite endpoint of "ability to thrive." Of the 22 patients, nine (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.
- In STR1VE-US, patients achieved rapid and sustained improvement in motor function unseen in natural history. CHOP INTEND scores increased by an average of 6.9 points at one month (N=22), 11.7 points at three months (N=22) and 14.6 points at six months (N=20) after gene therapy treatment. Twenty-one patients (95.5%) achieved a CHOP INTEND score ≥40, and 14 (63.6%) achieved a CHOP INTEND score ≥50.

STR1VE-EU

Phase 3, single-arm trial (STR1VE-EU) of infants with **Type 1 SMA**

- 1 death was reported by the manufacturer and attributed to severe respiratory infection with neurological complications and may be treatment related. An autopsy has been performed but results are not known publicly. Study completion date is September 11, 2020 (Final data collection date for primary outcome measure). As of November 2020, no study results have been posted on ClinicalTrials.gov for this study
- Interim data from the ongoing Phase 3 STR1VE-EU clinical trial for Zolgensma suggests the drug provides "significant therapeutic benefit", including event-free survival; rapid and sustained improvement in motor function; and motor milestone achievement, for patients with SMA Type 1. The data was presented during the World Muscle Society (WMS) 2020 Virtual Congress.

SPR1NT Pre-Symptomatic Study of Intravenous AVXS-101 in SMA for Patients with Multiple Copies of SMN2
Phase 3, open-label, single-arm, single-dose, study of AVXS-101 (gene replacement therapy) in patients with SMA

- Presymptomatic patients 6 weeks of age or less with SMA and 2 or 3 copies of SMN2 were treated
- **After a median follow-up of 5.4 months, all 18 children were alive and "event free"**
- **All treated children have survived to a median age of 6.1 months, and 4 are able to sit unsupported for at least 30 seconds, with 1 able to stand with assistance.**
- **Among 8 patients with two copies of SMN2, all reportedly achieved age-appropriate motor milestones including 4 who could sit without support and 1 who could stand with assistance.** All have achieved a CHOP-INTEND score of 50 points, with 6 achieving 60 points and 3 reaching the maximum score of 64 points.
- Serious adverse events were cases of croup (n=1), lethargy (n=1), and hypercalcemia (n=1), all of which resolved and were considered unrelated to treatment by investigators. Other observed adverse events included elevated transaminases, elevated blood creatine phosphokinase MB and elevated troponin.
- Patients with 2 copies of *SMN2* reached age-appropriate motor milestones, including 4 patients who could sit without support for at least 30 seconds according to Bayley-III Gross Motor criteria, and one patient who could stand with assistance for >=2 seconds. Untreated natural history indicates that patients with two copies

of *SMN2* will never sit without assistance. The median duration of follow-up is 5.4 months and the median age is 6.1 months.

- ***As of March 8, 2019***: All patients (18/18) were alive and event-free. Among patients with two copies of *SMN2* (n=8), a mean 8.9-point improvement from baseline in CHOP-INTEND was achieved one-month post dosing, and a mean score of 8.4 points in Bayley-III Gross Motor was achieved by month two. All patients in this group achieved or maintained a CHOP-INTEND score of 50 points, with six patients achieving a score of 60 points and three patients achieving the maximum score of 64.
- **Interim data reported for the first time from SPR1NT in pre-symptomatic SMA showed age-appropriate motor milestone achievement.** Patients treated with ZOLGENSMA before the onset of symptoms are achieving age-appropriate motor milestones in line with normal development. The SPR1NT data reinforce the potential ZOLGENSMA has as a foundational treatment for patients with SMA.

STRONG: Study of Intrathecal Administration of AVXS-101 for Spinal Muscular Atrophy

Phase 1, open-label, dose-comparison, multi-center trial designed to evaluate the safety and tolerability of one-time administration of ZOLGENSMA in patients with SMA Type 2 who have three 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.

- Evaluating the intrathecal delivery of ZOLGENSMA in patients with SMA Type 2
- 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.
- **Data as of March 8, 2019:** Interim data reported for the first time from STRONG in SMA Type 2 showed rapid motor function gains and milestone achievements with intrathecal ZOLGENSMA (onasemnogene abeparvovec; AVXS-101)

The best available published evidence to date on ZOLGENSMA is from the START Trial *(Hayes 2020)*
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 (completed; START). In both trials, Zolgensma was delivered as a single-dose intravenous 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 intravenous 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.

At this time, several 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 become available. **Refer to 'Ongoing Trials' discussion in the Summary of Clinical Evidence' section of policy.**

CLINICAL PRACTICE GUIDELINES

NOTE: ZOLGENSMA has not been addressed in practice guidelines as of this writing in May 2019

American Academy of Neurology (AAN)

At the 2019 American Academy of Neurology (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.

Spinal Muscular Atrophy 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 onasemnogene abeparvovec.

- 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 two or three 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 three 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 four SMN2 gene copies should receive immediate treatment. Also, patients with five (or more) SMN2 gene copies should be observed and screened for symptoms (Glascock 2020)

<u>2020 European Neuromuscular Expert Ad-Hoc Consensus Statement on Gene Replacement Therapy for Spinal Muscular Atrophy (Kirschner J, 2020)</u>

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 presymptomatic patients SMN2 copy number is the most important predictor of clinical severity and age of onset. As long as no better biomarkers or predictors are available, treatment decisions for presymptomatic patients should primarily be based on SMN2 copy number. Determination of SMN2 copy number needs to be performed in an expert laboratory with adequate measures of quality control.
- Consensus statement 3: 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 presymptomatic stage of the disease – is associated with markedly better outcome as compared to later start of treatment. Spinal muscular atrophy 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.

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.

DEFINITIONS

N/A

APPENDIX

APPENDIX 1: Clinical Classification of Spinal Muscular Atrophy

Disease phenotypes are classified according to a scheme developed at the 1991 International Consortium on Spinal Muscular Atrophy 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):

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.*
- *De Sanctis R, Pane M, Coratti G, et al. Clinical phenotypes and trajectories of disease progression in type 1 spinal muscular atrophy. Neuromuscular disorders: NMD. 2018;28(1):24-28.*

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.).

APPENDIX 2: Assessment Tools for Motor Development

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 INFORMATION

The codes listed in the policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

CPT	Description

HCPCS	Description
J3399	Injection, Onasemnogene abeparvovec-xioi, per treatment, up to 5x1015 vector genomes

ICD-10	Description
G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]
G12.1	Other inherited spinal muscular atrophy
G12.9	Spinal muscular atrophy, unspecified

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Policy History	P&T
Policy Developed Peer Review: AMR Peer Review Network. 6/7/2019. Practicing Physician. Board certified in Neurology, Sleep Medicine Peer Review: AMR Peer Review Network. 6/10/2019. Practicing Physician. Board certified in Pediatrics, Neurology with Special Qualification in Child, Neurodevelopmental Disabilities	6/18/2019
Revision Peer Review: AMR Peer Review Network. 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 (1) months 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)	Q4 2020

**All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence. Coverage criteria for Initial and Continuation of Therapy were revised/updated as appropriate.*