MEDICAL COVERAGE POLICY	
SERVICE: 253 - Onasemnogene Abeparvovec (Zolgensma®)	
Policy Number:	
Effective Date:	**10/01/2021**
Last Review:	**08/26/2021**
Next Review Date:	**08/26/2022**

Important note:
Unless otherwise indicated, this policy will apply to all lines of business.
Even though this policy may indicate that a particular service or supply may be considered medically necessary and thus covered, this conclusion is not based upon the terms of your particular benefit plan. Each benefit plan contains its own specific provisions for coverage and exclusions. Not all benefits that are determined to be medically necessary will be covered benefits under the terms of your benefit plan. You need to consult the Evidence of Coverage (EOC) or Summary Plan Description (SPD) to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and your plan of benefits, the provisions of your benefits plan will govern. However, applicable state mandates will take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, Federal mandates will apply to all plans. With respect to Medicare-linked plan members, this policy will apply unless there are Medicare policies that provide differing coverage rules, in which case Medicare coverage rules supersede guidelines in this policy. Medicare-linked plan policies will only apply to benefits paid for under Medicare rules, and not to any other health benefit plan benefits. CMS's Coverage Issues Manual can be found on the CMS website. Similarly, for Medicaid-linked plans, the Texas Medicaid Provider Procedures Manual (TMPPM) supersedes coverage guidelines in this policy where applicable.

SERVICE: Onasemnogene Abeparvovec (Zolgensma®)

PRIOR AUTHORIZATION: Required

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for coverage details.

For Medicare plans, please refer to appropriate Medicare LCD (Local Coverage Determination). If there is no applicable LCD, use the criteria set forth below.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid TMPPM.

Onasemnogene Abeparvovec (Zolgensma®) may be medically necessary for the treatment of Type 1 spinal muscular atrophy (SMA) when the following criteria are met:

1. Member is less than 6 months of age, OR,
   Member is greater than 6 months of age, less than 2 years of age, AND (both)
   - Patient has previously received nusinersen (Spinraza) for the treatment of Type I SMA with positive clinical response, AND
   - Member weighs less than 8 kg.
2. Member has genetically confirmed mutation or deletion of genes in chromosome 5q resulting in either: homozygous gene deletion or mutation (e.g., homozygous deletion of exon 7 at locus 5q13); or compound heterozygous mutation (e.g., deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 [allele 2]).
3. The diagnosis of Type 1 SMA has been made by a pediatric neurologist with expertise in the diagnosis of SMA.
4. Member has baseline anti-AAV9 antibody titers of ≤1:50 as measured by ELISA
5. Member is NOT invasive-ventilator dependent or not dependent on use of non-invasive ventilation beyond use for naps and nighttime sleep.
6. Patient has received prophylaxis against respiratory syncytial virus (RSV)
7. Therapy with nusinersen (Spinraza) or risdiplam (Evrysdi), if applicable, will be discontinued.

Exclusion criteria:

1. Active viral infection
2. Use of invasive ventilatory support or pulse oximetry <95% saturation

3. Concomitant use of any of the following drugs:
   - Drugs for treatment of myopathy or neuropathy
   - Agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy or immunosuppressive therapy within 3 months of starting treatment (e.g. corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, intravenous immunoglobulin, rituximab)
4. Member is not symptomatic or has Types 2, 3, or 4.
5. Member has advanced SMA (e.g., complete paralysis of limbs, permanent ventilator-dependence).

Zolgensma® is NOT proven or medically necessary for:

- The treatment of pre-symptomatic patients diagnosed by newborn screening who are unlikely to develop SMA;
- The treatment of symptomatic later-onset SMA beyond 2 years of age;
- SMA without chromosome 5q mutations or deletions;
- The routine combination treatment of SMA with concomitant survival motor neuron (SMN) modifying therapy, e.g., nusinersen (Spinraza) or risdiplam (Evrysdi).

Only ONE dose per lifetime is medically necessary.

All requests will be reviewed by a clinical pharmacist and medical director.

OVERVIEW:

Spinal Muscular Atrophy (SMA) is caused by a defective or missing SMN1 gene. Without a functional SMN1 gene, infants with SMA Type 1 rapidly lose the motor neurons responsible for muscle functions such as breathing, swallowing, speaking and walking. Left untreated, the child's muscles become progressively weaker eventually leading to paralysis or death, in most cases by his or her second birthday. Delivered as a single, one-time infusion, this technology works by replacing the missing or defective SMN1 gene with a functional copy that makes SMN protein, thereby improving motor neuron function and survival.

START was a Phase 1 study evaluating safety and efficacy of onasemnogene abeparvovec in SMA Type 1 patients genetically tested to confirm bi-allelic SMN1 deletions, 2 copies of survival motor neuron 2 (SMN2), negative findings for the c.859G>C modification in exon 7 and with the onset of clinical symptoms before 6 months of age. Onasemnogene was delivered intravenously during a single-dose infusion in patients 0.9 to 7.9 months of age. Two cohorts were dosed: Cohort 1 (n=3) received the low dose used in this study and Cohort 2 (n=12) received the high dose used in this study.

At the 24-month follow up, all 15 patients (100%), who were over all 24 months of age, were event-free, as opposed to only 8% of patients in a natural history study. This indicates a significant and clinically meaningful increase in overall survival for patients infused with onasemnogene when compared to untreated patients. At two years following infusion, no patient deaths were reported. The most commonly observed side effect in the onasemnogene clinical trial was elevated liver enzymes.

The reported study outcomes reflect Cohort 2 and includes follow-up of all patients out to 24 months following onasemnogene infusion. Patients in Cohort 2 consistently achieved and maintained key

developmental motor milestones. At 24 months of follow-up post-infusion, 11 patients (91.7%) were able to hold their head erect for >= 3 seconds and sit without support for >= 5 seconds, 10 patients (83.3%) were able to sit without support for >= 10 seconds, 9 patients (75.0%) were able to sit without support for >= 30 seconds and 2 patients each (16.7%) were able to stand alone, walk with assistance and walk alone.

STR1VE was an open-label, single-arm, single-dose, phase 3 trial done at 12 hospitals and universities in the USA evaluating the safety and efficacy of onasemnogene abeparvovec in symptomatic patients (identified through clinical examination) with infantile-onset spinal muscular atrophy. Coprimary efficacy outcomes were independent sitting for 30 s or longer (Bayley-III item 26) at the 18 month of age study visit and survival (absence of death or permanent ventilation) at age 14 months. 13 (59%, 97·5% CI 36-100) of 22 patients achieved functional independent sitting for 30 s or longer at the 18 month of age study visit (vs 0 of 23 patients in the untreated PNCR cohort; p<0·0001). 20 patients (91%, 79-100]) survived free from permanent ventilation at age 14 months (vs 6 [26%], 8-44; p<0·0001 in the untreated PNCR cohort).

Results from the STR1VE trial build on findings from the phase 1 START study by showing safety and efficacy of commercial grade onasemnogene abeparvovec. Onasemnogene abeparvovec showed statistical superiority and clinically meaningful responses when compared with observations from the PNCR natural history cohort for infantile-onset spinal muscular atrophy type 1.

MANDATES: None

SUPPORTING DATA:

CODES:

Important note:

CODES: Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.

CPT Codes:	
CPT Not Covered:	
HCPCS Codes:	J3399
ICD10 codes:	G12.0 Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann] G12.1 Other inherited spinal muscular atrophy G12.9 Spinal muscular atrophy, unspecified
ICD10 Not covered:	

CMS:

POLICY HISTORY:

Status	Date	Action
New	06/27/2019	New policy
Updated	08/28/2019	Age for use clarified and specific exclusions listed.
	06/29/2020	Logo changed to include FC
Reviewed	08/27/2020	Update to request reviewer and added HCPCS code

Reviewed	08/26/2021	Updated criteria to add risdiplam to SMN modifying therapy and overview

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. SWHP will continue to review clinical evidence related to this policy and may modify it at a later date based upon the evolution of the published clinical evidence. Should additional scientific studies become available and they are not included in the list, please forward the reference(s) to SWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

1. Mendell, JR., Al-Zaidy S., Shell R., et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med 2017; 377:1713-1722.
2. Farrar MA, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol. 2017; 81(3):355-368.
3. Anderton RS and Mastaglia FL. Advances and challenges in developing a therapy for spinal muscular atrophy. Expert Rev Neurother. 2015;15(8):895-908
4. Finkel RS, McDermott MP, Kaufmann P. et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014;83(9):810-7.
5. Mendell JR, Al Zaidy S, Shell R., et al. AVXS-101 Phase 1 Gene Replacement Therapy Clinical Trial in SMA Type 1: Event-Free Survival and Achievement of Developmental Milestones After 24 Months Post-Dosing. April 2018.
6. Day, John W et al. “Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial.” The Lancet. Neurology vol. 20,4 (2021): 284-293.