MEDICAL COVERAGE POLICY	
SERVICE:	**Onasemnogene Abeparvovec (Zolgensma®)**
Policy Number:	**253**
Effective Date:	**11/01/2024**
Last Review:	**08/12/2024**
Next Review:	**08/12/2025**

Important note: *Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.*

SERVICE: Onasemnogene Abeparvovec (Zolgensma®)

PRIOR AUTHORIZATION: Required

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

For Medicare plans, please refer to appropriate Medicare NCD (National Coverage Determination) or LCD (Local Coverage Determination). Medicare NCD or LCD specific InterQual criteria may be used when available. If there are no applicable NCD or LCD criteria, use the criteria set forth below.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid Provider Procedures Manual | TMHP (TMPPM). Texas Mandate HB154 is applicable for Medicaid plans.

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 2 years of age
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 neurologist with expertise in the diagnosis of SMA.
4. Member has baseline anti-AAV9 antibody titers of ≤1:50 as measured by ELISA
5. The dosing of onasemnogene abeparvovec (Zolgensma®) is in accordance with FDA labeling
6. Member does NOT have any of the following:
    a. Invasive-ventilator dependency or dependent on use of non-invasive ventilation beyond use for naps and nighttime sleep.
    b. Use of invasive ventilatory support
    c. Active infection, either acute (ex. cold, flu, gastroenteritis, otitis media, bronchiolitis, etc) or chronic uncontrolled (ex. chronic active hepatitis B)
    d. Preexisting liver impairment defined as ALT, AST, or total bilirubin levels (except due to neonatal jaundice) greater than 2 times ULN.
    e. Concomitant use of ongoing immunosuppressive therapy or immunosuppressive therapy within 3 months of starting treatment (e.g. corticosteroids, cyclosporine,

tacrolimus, methotrexate, cyclophosphamide, intravenous immunoglobulin, rituximab)
   f. Asymptomatic SMA or Types 2, 3, or 4 SMA
   g. Advanced SMA (e.g., complete paralysis of limbs, permanent ventilator-dependence).
7. Patient has received prophylaxis against influenza and respiratory syncytial virus (RSV) if recommended by the American Academy of Pediatrics (AAP).
8. Therapy with nusinersen (Spinraza) or risdiplam (Evrysdi), if applicable, will be discontinued.

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.

BACKGROUND:

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.

Acute serious liver injury, acute liver failure and elevated aminotransferases can occur with onasemnogene abeparvovec. Acute serious liver injury and acute liver failure, including fatal cases, have been reported with onasemnogene abeparvovec use. Patients with preexisting liver impairment or acute hepatic viral infection may be at higher risk of acute serious liver injury/acute liver failure. Patients with ALT, AST, or total bilirubin levels (except due to neonatal jaundice) > 2 × ULN have not been studied in clinical trials with onasemnogene abeparvovec. Due to activation of humoral and cellular immunity following onasemnogene abeparvovec infusion, patients with underlying active infection, either acute (e.g., respiratory, gastrointestinal) or chronic uncontrolled (e.g., chronic active hepatitis B), could be at an increased risk of serious systemic immune response, potentially resulting in more severe clinical courses of the infection. Serious systemic immune response can present with a variety of findings (e.g., high fever, hypotension, etc.). Patients with infection were excluded from participation in onasemnogene abeparvovec clinical trials. To mitigate the risk of serious and life-threatening systemic immune response, administer systemic corticosteroids before and after onasemnogene abeparvovec infusion to patients who are clinically stable in their overall baseline health status (e.g., hydration and nutritional status, absence of infection) prior to infusion. Seasonal prophylaxis against influenza and respiratory syncytial virus (RSV) and vaccination status should be up-to-date prior to onasemnogene abeparvovec administration.

CODES:

Important note: *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:	
HCPCS Codes:	J3399 - Injection, onasemnogene abeparvovec-xioi, per treatment, up to 5x10^15 vector genomes
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:	

POLICY HISTORY:

Status	Date	Action
New	06/27/2019	New policy
Updated	08/28/2019	Age for use clarified and specific exclusions listed.
Updated	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
Updated	09/01/2022	Updated age limit criteria, added FDA dosing requirement, amended RSV criteria for AAP recommendation
Updated	08/24/2023	Combined all exclusion criteria to one section, added liver function exclusion and recommendation for influenza vaccine
Updated	08/12/2024	Applied new format and layout and updated background information

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and make modifications 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 BSWHP 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.
7. Zolgensma (onasemnogene abeparvovec) [prescribing information]. Bannockburn, IL: Novartis Gene Therapies, Inc. February 2023.

***Note**:*
Health Maintenance Organization (HMO) products are offered through Scott and White Health Plan dba Baylor Scott & White Health Plan, and Scott & White Care Plans dba Baylor Scott & White Care Plan. Insured PPO and EPO products are offered through Baylor Scott & White Insurance Company. Scott and White Health Plan dba Baylor Scott & White Health Plan serves as a third-party administrator for self-funded employer-sponsored plans. Baylor Scott & White Care Plan and Baylor Scott & White Insurance Company are wholly owned subsidiaries of Scott and White Health Plan. These companies are referred to collectively in this document as Baylor Scott & White Health Plan.

RightCare STAR Medicaid plans are offered through Scott and White Health Plan in the Central Managed Care Service Area (MRSA) and STAR and CHIP plans are offered through SHA LLC dba FirstCare Health Plans (FirstCare) in the Lubbock and West MRSAs.