DR.005.E ZOLGENSMA® (onasemnogene abeparvovec-xioi)

Original Implementation Date : 03/01/2020
Version [E] Date : 04/17/2024
Last Reviewed Date: 05/21/2025

PRODUCT VARIATIONS

This policy applies to all Jefferson Health Plans/Health Partners Plans lines of business unless noted below.

Gene therapy is a benefit exclusion for Individual and Family (ACA) product lines and therefore, non-covered.

POLICY STATEMENT

The plan considers ZOLGENSMA® medically necessary when the prior authorization criteria listed in the policy are met.

OFF-LABEL USE

Authorization for off-labeled use of medication will be evaluated on an individual basis. Review of an off-labeled request by the Medical Staff will be predicated on the appropriateness of treatment and full consideration of medical necessity. For off-label use Medical Directors will review scientific literature and local practice patterns.

FDA APPROVED INDICATIONS

ZOLGENSMA® is an adeno-associated virus vector-based gene therapy 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.

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PRIOR AUTHORIZATION CRITERIA

INITIAL CRITERIA

1. Medication is prescribed by or in consultation with a physician who specializes in the treatment of spinal muscular atrophy (SMA); and

2. Member has a documented diagnosis of SMA with the following: genetically confirmed bi-allelic *SMN1* gene deletions or variants; and

3. Member does not have a diagnosis of advanced SMA disease (complete limb paralysis, invasive ventilation support, etc.)? *If NO, go to 4. If YES, refer to Medical Director.*

4. If born premature, the member will not be given their ZOLGENSMA® infusion until the corresponding full-time gestational age is reached.

5. The member is less than 2 years of age.

6. The member has a baseline anti-adeno-associated virus serotype 9 (AAV9) antibody titer ≤1:50 measured by enzyme-linked immunosorbent assay (ELISA.

7. The member will be given systemic corticosteroids, administered beginning one day prior to infusion for a total of 30 days.

8. The member has documentation for baseline liver function tests (AST, ALT, total bilirubin, and prothrombin time), albumin, partial thromboplastin time (PTT), and INR, and they will continue to be monitored for at least 3 months after the infusion or until results are unremarkable.
9. The member has documentation of baseline platelet count and troponin-I levels and they will continue to be monitored.
10. The member does not have signs and symptoms of infection.

11. The member's dose is prescribed within the FDA labeled dose of 1.1×10^{14} vector genomes per kilograms (vg/kg) of body weight.

RENEWAL CRITERIA

ZOLGENSMA® is meant for a one-time-only dose. The safety and effectiveness of repeat administration of ZOLGENSMA® has not been evaluated.

DOSAGE AND ADMINISTRATION

ZOLGENSMA® is for single-dose intravenous infusion only:

- Recommended dosage: ZOLGENSMA® 1.1×10^{14} vector genomes (vg) per kg of body weight.
- Administer ZOLGENSMA® as an intravenous infusion over 60 minutes through a venous catheter.
- Requires premedication with systemic corticosteroids. Equivalent to oral prednisolone at 1 mg/kg per day beginning 1 day prior to infusion for a total of 30 days. At the end of the 30-day period of systemic corticosteroid treatment, check liver function by clinical examination and by laboratory testing. For patients with unremarkable findings, taper the corticosteroid dose gradually over the next 28 days. If liver function abnormalities persist, continue systemic corticosteroids (1 mg/kg/day) until findings become unremarkable, and then taper the corticosteroid dose gradually over the next 28 days or longer if needed. If liver function abnormalities continue to persist ≥ 2 × ULN after the 30-day period of systemic corticosteroids, promptly consult a pediatric gastroenterologist or hepatologist.

RISK FACTORS/SIDE EFFECTS

Most common adverse reactions (incidence ≥5%) noted in trials were elevated liver enzymes and vomiting.

Cardiac effects: transient increases in cardiac troponin-I level were observed after ZOLGENSMA® infusion; clinical importance is unknown. However, cardiac toxicity was observed in animal studies. Monitor troponin-I before and periodically after ZOLGENSMA® infusion until return to baseline.

Hepatic effects: acute serious liver injury and elevated aminotransferases were observed in clinical trials; assess liver function by clinical examination and laboratory testing. Administer systemic corticosteroids before and after ZOLGENSMA® infusion.

Systemic Immune Response: Due to activation of humoral and cellular immunity following ZOLGENSMA® infusion, patients with underlying active infection, either acute or chronic uncontrolled, could be at an increased risk of serious systemic immune response, potentially resulting in more severe clinical courses of the infection. Recommended increased vigilance in the prevention, monitoring, and management of infection before and after ZOLGENSMA® infusion. To mitigate risk of serious and life-threatening systemic immune response, administer ZOLGENSMA® to patients who are clinically stable in their overall baseline health status prior to infusion.

Thrombocytopenia: transient decreases in platelet count were observed at different time points through the trial after ZOLGENSMA® infusion. Monitor platelet counts before and periodically after ZOLGENSMA® infusion until return to baseline.

Thrombotic Microangiopathy (TMA): If clinical signs, symptoms and/or laboratory findings occur, consult a pediatric hematologist and/or pediatric nephrologist immediately to manage as clinically indicated.

Tumorigenicity: There is a theoretical risk of tumorigenicity due to integration of AAV vector DMS into the genome. Cases of tumor have been reported in patients who received ZOLGENSMA® post-approval.

MONITORING

Efficacy:

Physical findings:

- Achievement of developmental milestones (e.g., kicking, head control, rolling, sitting, crawling, standing, walking) may indicate efficacy.

Toxicity:

- Baseline: Liver function (clinical exam, AST, ALT, total bilirubin, and PT), CBC (Hb, platelet count), SCr, troponin-I, and anti-AAV9 antibody test.
- First month after treatment: Liver function (clinical exam, AST, ALT, total bilirubin, and PT), platelets, and troponin-I (check weekly); signs and symptoms of thrombotic microangiopathy (e.g., hypertension, bruising, decreased urine output, seizures).
- Second and third month after treatment: Liver function (clinical exam, AST, ALT, total bilirubin, and PT) every other week until AST/ALT are <2 × ULN, PT is normal, total bilirubin is normal, and clinical exam is normal; platelet count every other week until counts return to baseline, and troponin-I monthly until troponin-I level returns to baseline; signs and symptoms of thrombotic microangiopathy (e.g.,, hypertension, bruising, decreased urine output, seizures).

BLACK BOX WARNING

Acute serious liver injury and elevated aminotransferases can occur with ZOLGENSMA®.

CLINICAL EVIDENCE

In an open label single arm clinical trial(study 1) and an open label single arm ascending dose clinical trial(study 2), the efficacy of Zolgensma in pediatric patients less than 2 years of age with bi-allelic mutations in the SMN1 gene was evaluated. The patients included in the study experienced onset of clinical symptoms consistent with SMA before 6 months of age. Confirmed bi-allelic SMN1 gene deletions, 2 copies of the SMN2 gene, and absence of c.859G.C modification exon 7 of SMN2 gene. The baseline of all patients enrolled had anti-AAV9 titers of ≤ 1:50.

The assessment of efficacy for both trials was monitored by the basis of survival and achievement of developmental motor milestones. Survival was defined as time from birth to death or permanent ventilation. Permanent ventilation was defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in the absence of an acute reversible illness, excluding

perioperative ventilation. Efficacy was also supported by assessments of ventilator use, nutritional support and scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND). CHOP-INTEND is an assessment of motor skills in patients with infantile-onset SMA.

In study 1 there were 21 patients enrolled, 10 male and 11 female. Prior to treatment of Zolgensma none of the patients required noninvasive ventilator support or non-oral nutrition. The mean CHOP-INTEND baseline score was 31(range: 18-47). The mean age of the patients at the time of treatment was 3.9 months(range: 0.5 to 5.9 months). All patients enrolled received 1.1 x 10^{14} vg/kg of ZOLGENSMA.

By March 2019, data for this study was cut off, 19 patients were enrolled in the study and without permanent ventilation. One patient died due to disease progression at 7.8 months and one patient withdrew from the study at 11.9 months. The age range of the 19 surviving patients were from 9.4 months to 18.5 months. At the time of the data cutoff, 13 out of 19 patients reached 14 months old with no permanent ventilation. One of the co-primary efficacy endpoints found that 10 out of 21 patients were able to sit without support for ≥ 30 seconds between 9.2 and 16.9 months of age (mean age was 12.1 months)

In study 2 there were 15 patients enrolled 6 male and 9 females with infantile onset SMA. Patients were divided into two cohorts: low dose and high dose cohort. There were 3 patients enrolled in the low dose cohort and 12 patients in the high dose cohort. At the time of treatment, the mean age of the low dose cohort group was 6.2 months and 3.4 months in the high dose cohort. The dosage received by patients in the low-dose cohort was approximately one-third of the dosage received by patients in the high-dose cohort. The retrospectively estimated dosage range in the high-dose cohort is approximately 1.1 x 10^{14} to 1.4 x 10^{14} vg/kg.

After 24 months of Zolgensma infusion, 1 patient in the low dose cohort and all 12 patients in the high dose cohort met the permanent ventilation endpoint. All patients in the low dose cohort were not able to sit without support or stand/walk. From the high dose cohort 9 of the 12 were able to sit without support for ≥ 30 seconds, and 2 patients were able to stand and walk without assistance.

BACKGROUND

Spinal muscular atrophy (SMA) is a group of rare hereditary diseases caused by a genetic mutation in the *survival motor neuron 1 (SMN1)* gene. Typically, the *SMN1* gene encodes most of the survival motor neuron (SMN) protein within the body, whereas a smaller percentage of functional SMN protein is encoded by *the survival motor neuron 2 (SMN2)* gene. SMN protein is largely responsible for the health and normal function of specialized nerve cells called motor neurons. Motor neurons located on the brain and spinal cord control voluntary muscle movement; an insufficient amount of functional SMN protein leads to motor neuron death, muscle weakness, hypotonia and atrophy.

The SMA classification is determined based on a patient's age at disease onset, as well as by functional ability.

SMA Type	Age of Onset	Highest Functional Ability	Typical number of copies of *SMN2* gene present in majority of patients
Type I: Werdnig Hoffman	0-6 months	Never sits or rolls over	1-2 copies
Type II: intermediate	7-18 months	Sits, may stand, never walks	3 copies
Type III: mild, Kugelberg-Welander disease	≥ 18 months	Walks	3-4 copies
Type IV: adult	2nd or 3rd decade	Walks during adult years	4-6 copies

The diagnosis of SMA is based on molecular genetic testing of *SMN1/SMN2*; genetically confirmed bi-allelic deletions or variants of *SMN1* gene are diagnostic of SMA. The number of *SMN2* gene copies is not essential to diagnosis, but it will influence the severity of SMA.

218th European Neuromuscular Center (ENMC) International Workshop summarizes survival data from SMA Type 1 studies, concluding that the number of copies of *SMN2* gene is a strong predictive biomarker when looking at the rapidly declining survival curve for patient with 2 copies compared to those that have 3 copies of the *SMN2* gene.

Although current literature suggests there is a correlation between clinical phenotype/severity of disease and the number of copies of *SMN2* gene, the 2017 update for the consensus statement for standard of care in spinal muscular atrophy states that there are exceptions; in individual cases, the number of *SMN2* copies may not predict the severity of the phenotype.

CODING

Note*:* The Current Procedural Terminology (CPT®), Healthcare Common Procedure Coding System (HCPCS), and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes that *may* be listed in this policy are for reference purposes only. Listing of a code in this policy does not imply that the service is covered and is not a guarantee of payment. Other policies and coverage guidelines may apply. When reporting services, providers/facilities should code to the highest level of specificity using the code that was in effect on the date the service was rendered. This list may not be all inclusive.

CPT Code	Description
N/A	

HCPCS Code	Description
J3399	Injection, onasemnogene abeparvovec-xioi, per treatment, up to 5x10

ICD-10 Codes	Description
G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffman].
G12.1	Other inherited spinal muscular atrophy
G.12.9	Spinal muscular atrophy, unspecified

DISCLAIMER

Approval or denial of payment does not constitute medical advice and is neither intended to guide nor influence medical decision making. Policy Bulletins are developed by us to assist in administering plan benefits and constitute neither offers of coverage nor medical advice. This Policy Bulletin may be updated and therefore is subject to change. For Health Partners Plans Medicaid and Health Partners Plans Chip products: Any requests for services that do not meet criteria set in PARP will be evaluated on a case-by-case basis.

POLICY HISTORY

This section provides a high-level summary of changes to the policy since the previous version.

Summary	Version	Version Date
2025 Annual review. Product variation and disclaimer statement updated. Revisions made to Dosage, Risk factors/Side effects, Monitoring and Clinical evidence sections. References updated.	E	05/21/2025
2024 Annual review. Statement added to Black Box Warning section.	D	04/17/2024
2023 Annual review. Revisions were made to the following sections of the policy: Prior Authorization Criteria, Dosage and	C	06/23/2023

Administration, Black Box Warning. References were updated according.		
2022 Annual review. Thrombotic Microangiopathy added to the "Risk Factor" section.	B	07/01/2022
2021 Annual review. J3399 was added to the coding table.	A	03/01/2020
2020 Annual review. No changes.	A	03/01/2020
New Policy.	A	03/01/2020

REFERENCES

1. Al-Zaidy S, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. Pediatr Pulmonol. 2019 Feb; 54(2):179-185.

2. FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality [Internet]. U.S. Food and Drug Administration. FDA; [cited 2019 Sep 5]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease.

3. Finkle RS, et al, European Neuromuscular Center (ENMC) SMA Workshop Study Group (2017). 218th ENMC International Workshop: Revisiting the consensus on standards of care in SMA Naarden, The Netherlands, 19-21 February 2016. Neuromuscular Disorders. 2017 Jun; 27(6):596-605.

4. Mercuri E, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscular Disorders. 2018 ;(28): 103–115.

5. National Institutes of Health Spinal Muscular Atrophy Fact Sheet. National Institute of Neurological Disorders and Stroke. May 2019. *NIH Publication No. 19-NS-5597.Available from:* https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Spinal-Muscular-Atrophy-Fact-Sheet.

6. ZOLGENSMA ® [prescribing information]. AveXis Inc., Bannockburn, IL. 2/2023. Last viewed 2/20/2024.

7. Spinal Muscular Atrophy, Olaf Bodamer, MD, PhD, UpToDate, Literature review current through Jan. 2025.