DR.005.G ZOLGENSMA® (onasemnogene abeparvovec-xioi) and ITVISMA® (onasemnogene abeparvovec-brve)

Original Implementation Date: 03/01/2020
Version {G} Date: 11/02/2026
PARP Approved Date: 09/03/2026
Last Reviewed Date: 09/16/2026

Thank you for being a valued provider for members in one or more of our health plans: Jefferson Health Plans Medicare Advantage, Jefferson Health Plans Individual and Family Plans, Jefferson Health Plans CHIP, and/or Jefferson Health Plans EverWell (our Medicaid plan).

PRODUCT VARIATIONS

This policy applies to all Jefferson Health 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® and ITVISMA® 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 (AVV) 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.

Itvisma® is an adeno-associated virus (AVV) vector-based gene therapy indicated for the treatment of spinal muscular atrophy (SMA) in adults and pediatric patients 2 years of age and older with confirmed mutation in survival motor neuron 1 *(SMN1)* gene.

Onasemnogene abeparvovec is a recombinant adeno-associated virus vector-based (AAV9-based) gene therapy designed to deliver a copy of the gene encoding the human SMN protein for treatment of spinal muscular atrophy (SMA). SMA is caused by a bi-allelic mutation in the *SMN1* gene, which results in insufficient SMN protein expression. Onasemnogene abeparvovec is marketed under the names Zolgensma® and Itvisma®, both developed by Novartis Gene Therapies, Inc. While Zolgensma® and Itvisma® contain the same active ingredient, their primary differences lie in the FDA-approved age range for patients and the method of administration.

Limitation of use:

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

PRIOR AUTHORIZATION CRITERIA

Initial Criteria- Onasemnogene abeparvovec-xioi (Zolgensma)®

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; **and**

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

5. The member is less than 2 years of age; **and**

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

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

8. The member has documentation for baseline liver function tests (AST, ALT, total bilirubin, and albumin), prothrombin time, 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; **and**

9. The member has documentation of baseline platelet count and troponin-I levels and they will continue to be monitored; **and**

10. The member does not have signs and symptoms of infection; **and**

11. The member has not received any prior doses of ZOLGENSMA®; **and**

12. If the member is treated with Nusinersen(Spinraza), or Risdiplan(Evrysdy) it will be discontinued prior to the treatment with *Onasemnogene abeparvovec xioi (Zolgensma);* **and**

13. The member's dose is consistent with the FDA approved dose of 1.1×10^{14} vector genomes per kilograms (vg/kg) of body weight.

Initial Criteria- *Onasemnogene abeparvovec- brve (Itvisma)*

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 is greater than or equal to 2 years of age the time of treatment; **and**

4. Member does not have a diagnosis of advanced SMA disease (invasive ventilation support, tracheostomy etc; **and**

5. Member does not have contraindication for lumbar puncture (for example increased intracranial pressure); **and**

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

7. Member will be given systemic corticosteroids, administered beginning one day prior to infusion for a total of 30 days; **and**

8. Member has documentation for baseline liver function tests (AST, ALT, total bilirubin, and albumin), prothrombin time, 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; **and**

9. Member has documentation of baseline platelet count and troponin-I levels and they will continue to be monitored; **and**

10. Member does not have signs and symptoms of infection; **and**

11. Member has not received any prior doses of ZOLGENSMA®; **and**

12. If the member is treated with Nusinersen(Spinraza®), or Risdiplan(Evrysdy) it will be discontinued prior to the treatment with *Onasemnogene abeparvovec- brve (Itvisma)*.

13. Member's dose is consistent with the FDA approved dose of 1.1×10^{14} vector genomes per kilograms (vg/kg) of body weight.

RENEWAL CRITERIA

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

DOSAGE AND ADMINISTRATION

ZOLGENSMA® is available as a suspension for intravenous infusion, supplied as single-use vials. ZOLGENSMA® is provided in a kit containing 2 to 14 vials, as a combination of 2 vial fill volumes (either 5.5 mL or 8.3 mL). All vials have a nominal concentration of 2.0×10^{13} vector genomes (vg) per mL. ZOLGENSMA® is intended for single-dose intravenous infusion only. The recommended dosage of ZOLGENSMA® is 1.1×10^{14} vector genomes (vg) per kg of body weight.

ZOLGENSMA® is administered as an intravenous infusion over 60 minutes through a venous catheter.

The administration of Zolgesma® requires premedication with systemic corticosteroids.

See Full Prescribing Information for complete dosage and administration recommendations.

Itvisma® is a suspension for intrathecal injection, supplied in single-dose vials. Each single-dose vial contains 1.2×10^{14} vg of onasemnogene abeparvovec in 3 mL of suspension. Itvisma® has a nominal concentration of 4×10^{13} vg/mL, and each vial contains an extractable volume of not less than 3 mL. Itvisma is intended for single-dose intrathecal injection only.

The recommended dosage of Itvisma is 1.2×10^{14} vector genomes (vg) as an intrathecal bolus injection over approximately 1 to 2 minutes.

See Full Prescribing Information for complete dosage and administration recommendations.

RISK FACTORS/SIDE EFFECTS

Onasemnogene abeparvovec-xioi **(Zolgensma)**®

Most common adverse reactions (incidence ≥5%) were elevated aminotransferases and vomiting.

Zolgensma® (onasemnogene abeparvovec-xioi) carries a boxed warning for serious liver injury and acute liver failure, with reports of fatal outcomes associated with these conditions and elevated aminotransferases. To mitigate potential elevations in aminotransferases, systemic corticosteroids should be administered before and after the Zolgensma® injection.

Other warnings: Cardiac effects and Elevated Troponin I; Acute Serious Liver Injury; Acute Liver Failure or Elevated Aminotransferases; Systemic Immune Response; Thrombocytopenia; Thrombotic Microangiopathy (TMA); AAV Vector Integration and Risk of Tumorigenicity; Infusion-Related Reactions.

For full detail, please refer to package labeling.

Onasemnogene abeparvovec-brve (**Itvisma**)®

Most common adverse reactions (incidence ≥ 10%) were upper respiratory tract infection, upper gastrointestinal symptoms, pyrexia, and headache.

Itvisma® carries a boxed warning for acute serious liver injury and elevated aminotransferases. To mitigate potential elevations in aminotransferases, systemic corticosteroids should be administered before and after the Itvisma® injection.

Other warnings: Thrombocytopenia; Thrombotic Microangiopathy (TMA); Cardiac effects and Elevated Troponin I; Peripheral sensor neuropathy.

For full detail, please refer to package labeling.

MONITORING

Per package labeling.

®

BLACK BOX WARNING

Serious liver injury and acute liver failure with fatal outcomes have been reported. Acute serious liver injury and elevated aminotransferases can occur with ZOLGENSMA® and Itvisma®.

CLINICAL EVIDENCE

On May 24, 2019, The U.S. Food and Drug Administration (FDA) approved Zolgensma® (onasemnogene abeparvovec-xioi) the first gene therapy approved to treat children less than two years of age with spinal muscular atrophy (SMA).

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 was 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.

On November 24, 2025, the U.S. FDA approved Itvisma® (onasemnogene abeparvovec-brve) for the treatment of SMA in adult and pediatric patients 2 years of age and older with confirmed mutation in the survival motor neuron 1 *(SMN1)* gene. Approval is supported by "substantial evidence" of effectiveness from a well-controlled Phase 3 study, along with confirmatory data on the product's mechanism of action and efficacy findings from Zolgensma, which shares the same active ingredient but is administered intravenously to younger patients.

Itvisma® contains the same active ingredient as Zolgensma® but is formulated at a different concentration for direct administration into the central nervous system through a single intrathecal injection, regardless of patient weight. This approach enables targeted delivery to motor neurons with a lower vector dose, resulting in

a rapid onset of action that addresses the genetic root cause of SMA by restoring SMN protein production and halting disease progression.

The FDA review team leveraged safety data from Zolgensma®, finding that most side effects of Itvisma® are consistent with those associated with Zolgensma®.

Proud et al. (2025) conducted the STEER trial (NCT05089656), a 52-week, phase 3, multicenter, randomized, sham-controlled, double-blind study that evaluated intrathecal onasemnogene abeparvovec (OAV101 IT), a one-time gene transfer therapy, in patients with spinal muscular atrophy (SMA). The study included treatment-naive participants aged 2 to less than 18 years who were able to sit but had never walked independently.

The study excluded participants with who required invasive ventilation, awake noninvasive ventilation for more than 6 hours in a 24-hour period, noninvasive ventilation for over 12 hours in a 24-hour period, or those needing a tracheostomy.

The primary efficacy endpoint was the change from baseline in the Hammersmith Functional Motor Scale-Expanded (HFMSE) score. A total of 126 patients were enrolled, with 75 receiving OAV101 IT and 51 undergoing a sham procedure. The primary endpoint was achieved. Patients treated with OAV101 IT had a significant increase in HFMSE score compared to the sham group (least squares mean difference of 1.88, 95% confidence interval: 0.51-3.25; P = 0.0074). The overall incidence of adverse events was comparable between the two groups. Increases in transaminases were infrequent. Two participants in the OAV101 IT group and one in the sham group experienced sensory symptoms. Overall, the one-time administration of OAV101 IT resulted in a statistically significant improvement in motor function compared to the sham control, with acceptable safety findings reflected in similar rates of AEs, SAEs, and AESI across both groups.

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, KugelbergWelander 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® is a registered trademark of the American Medical Association.

CPT Code	Description
N/A	N/A

HCPCS Code	Description
J3399	Injection, onasemnogene abeparvovec-xioi, per treatment, up to 5x10
J3405	Injection, onasemnogene abeparvovec-brve, per treatment

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 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 Jefferson Health Plans EverWell and Jefferson Health 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
2026 Adhoc review. HCPCS code J3405 added to policy with FDA approved indications, Prior Authorization Criteria, Dosage and Administration, Risk factors/Side effects Monitoring, Black Box Warning, and Clinical Evidence Sections. References updated.	G	11/02/2026
2026 Annual Review. Revisions made to FDA approved indications, Prior Authorization Criteria, Dosage and Administration, Risk factors/Side effects Monitoring and Black Box Warning Sections. References updated.	F	04/15/2026
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 Administration, Black Box Warning. References were updated according.	C	06/23/2023
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):179185.

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]. https://www.fda.gov/news-events/press-announcements/fda-approvesinnovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-raredisease

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/PatientCaregiver-Education/Fact-Sheets/Spinal-Muscular-Atrophy-Fact-Sheet.

6. ZOLGENSMA® (onasemnogene abeparvovec-xioi) prescribing information, Novartis Gene Therapies, Inc., Feb. 2025. Available from: https://www.novartis.com/us-en/sites/novartis_us/files/zolgensma.pdf

7. Spinal Muscular Atrophy- Olaf Bodamer, MD, PhD, UpToDate, last updated: **Mar 16, 2026**

8. Itvisma® package insert (onasemnogene abeparvovec-brve): https://www.fda.gov/media/189857/download