STATE OF IOWA DEPARTMENT OF
Health AND Human
SERVICES

Zolgensma (onasemnogene abeparvovec-xioi)
PAM-017

Iowa Medicaid Program:	Prior Authorization	**Effective Date:**	01/01/2021
Revision Number:	4	**Last Rev Date:**	01/19/2024
Reviewed By:	Medicaid Medical Director	**Next Rev Date:**	01/17/2025
Approved By:	Medicaid Clinical Advisory Committee	**Approved Date:**	10/16/2020

Overview

Medication:[1]	onasemnogene abeparvovec-xioi
Brand Name:	Zolgensma®
Pharmacologic Category:	Adeno-associated virus vector-based (AAV) gene therapy

FDA-Approved Indication(s):	• 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 have not been established.
	  ○ Use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

How Supplied:	• Suspension for intravenous infusion • Provided in a kit containing 2 to 9 vials • Vials are provided in one of two fill volumes, either 5.5 mL or 8.3 mL
Dosage and Administration:	• 1.1×10^{14} vector genomes per kilogram (vg/kg) of body weight • Administered as an IV infusion over 60 minutes
Benefit Category:	Medical

BOXED WARNING: SERIOUS LIVER INJURY AND ACUTE LIVER FAILURE

- Cases of acute liver failure with fatal outcomes have been reported. Acute serious liver injury and elevated aminotransferases can also occur with Zolgensma®.
- Patients with preexisting liver impairment may be at higher risk.
- Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing. Administer systemic corticosteroid to all patients before and after Zolgensma® infusion. Continue to monitor liver function for at least 3 months after infusion, and at other times as clinically indicated.

Descriptive Narrative

Spinal muscular atrophy (SMA), an autosomal recessive genetic disorder, affects 1 in 10,000 live births and is the most common genetic cause of infant mortality. The majority of cases (over 95 percent) are caused by a homozygous deletion of *SMN1* gene, which encodes the survival motor neuron (SMN) protein.[2] Loss or mutation of both copies of the *SMN1* gene causes SMA. Critical deficiency of SMN protein results in degeneration of motor neurons in the spinal cord, resulting in progressive muscle weakness and atrophy. Weakness and loss of response to stimuli in the lower extremities are most common, but in severe cases, the muscles that control the mouth, throat, and respiration may also be impacted.[3]

In combination with loss of *SMN1*, patients retain variable numbers of copies of a second similar gene, *SMN2*, which produce reduced levels of the survival motor neuron (SMN) protein that are insufficient for normal motor neuron function.[4] A higher number of copies of *SMN2* often correlates to milder disease, but this correlation is a relative and not an absolute one.[5]

Zolgensma® (onasemnogene abeparvovec-xioi) is a recombinant AAV9-based gene therapy designed to deliver a copy of the gene encoding the human SMN protein. In human case studies, intravenous (IV) administration of Zolgensma® resulted in cell transduction and expression of the SMN protein.

Spinal muscular atrophy has traditionally been classified into types 0-4 based on symptom severity and genotype, but with new therapies available (including nusinersen, risdiplam, and onasemnogene abeparvovec-xioi), phenotypes have become more diverse and classifications have evolved to focus on functional status or treatment response.

Classification of Spinal Muscular Atrophy[6]

SMA Type	Copies SMN2	Onset	Motor Milestones	Clinical Features	Natural History Prior to Disease-Modifying Therapy
0	1	Prenatal, at birth	Non-sitter, no head control	Generalized weakness, hypotonia, respiratory failure, poor feeding, contractures	Death within weeks of birth
1	1-2	0-6 months	Non-sitter	Proximal predominant weakness, respiratory insufficiency, poor feeding, tongue fasciculations	Death by age 2
2	3	6-18 months	Sits independently, never stands or ambulates	Proximal predominant weakness, tongue fasciculations, minipolymyoclonus, scoliosis	Most alive at 25 years
3	3-4	3a: 18 months – 3 years 3b: 3 – 30 years	Ambulates independently	Proximal, abnormal gait, lower extremity predominant weakness	Normal lifespan
4	4 or more	>30 yr	Ambulates independently	Maintain ability to ambulate	Normal lifespan

Guidelines

In 2018, the Cure SMA[7] Newborn Screening (NBS) Multidisciplinary Working Group (consisting of 15 clinicians and geneticists with SMA experience) formulated a treatment algorithm for infants with a positive SMA NBS test. The recommendation at that time was that all infants with two or three copies of *SMN2* should receive immediate treatment. 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.

The working group acknowledged that current laboratory assays designed to detect *SMN2* copy number often have difficulty distinguishing high copy numbers, and that many labs report results as four or more copies, being unable to give an exact number. Recognizing this fact, the group encouraged follow-up with a laboratory able to distinguish exact *SMN2* copy number.[8]

In September 2019, this working group reconvened to reassess the treatment algorithm for newborns with SMA identified through newborn screening based upon new experience and therapeutic options. The working group updated their position to a recommendation for immediate treatment for infants diagnosed with SMA via NBS with four copies of *SMN2*.

The working group also revisited the published recommendation to wait to treat for infants with five copies of *SMN2* and unanimously voted to uphold the recommendation of watchful waiting.[9] Although the 2019 working group did not revisit the topic of the accuracy of laboratory assays in distinguishing high copy numbers of *SMN2*, more recent information supports that many laboratories are now able to provide more concise results regarding copy numbers.

Criteria

Prior authorization is required.

Zolgensma® is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of spinal muscular atrophy (SMA), with **BOTH** of the following:
    a. Genetic documentation of bi-allelic mutations in the *survival motor neuron 1 gene (SMN1)*, either deletions or point mutations; **AND**
    b. Documentation of laboratory results confirming that the member has 4 or less copies of the *survival motor neuron 2 gene (SMN2)*; **AND**
    c. Anti-adeno-associated viral vector, serotype 9 (AAV9) antibody titer is less than or equal to 1:50; **AND**
2. Member is less than 2 years of age at the time of administration of Zolgensma® and full-term gestational age has been reached (if neonatal member born prematurely); **AND**
3. Treatment is prescribed by, or in consultation with, a physician who specializes in the treatment of spinal muscular atrophy and/or neuromuscular disorders; **AND**
4. The member has not previously received treatment with Zolgensma®; **AND**
5. The member is not currently being treated with nusinersen (Spinraza®) OR treatment with nusinersen will be discontinued prior to administration of Zolgensma®; **AND**
6. The member is not currently being treated with risdiplam (Evrysdi®) OR treatment with risdiplam will be discontinued prior to administration of Zolgensma®; **AND**
7. Member does not have findings of advanced SMA, including but not limited to, complete paralysis of limbs, invasive ventilator support (tracheostomy), or respiratory assistance for 16 or more hours per day (beyond use for naps and nighttime sleep); **AND**
8. Dose does not exceed a single administration of 1.1×10^{14} vector genomes per kilogram (vg/kg) of body weight.

Approval Duration and Quantity Limits

	Initial Authorization	Subsequent Authorization(s)
Approval Duration	One course of treatment per lifetime, to be administered prior to member turning 2 years of age	Not applicable
Quantity Limits	One-time dose, not to exceed 1.1×10^{14} vector genomes per kilogram (vg/kg) of body weight	

Coding and Product Information

The following list(s) of codes and product information are provided for reference purposes only and may not be all inclusive. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment, nor does the exclusion of a code imply that its association to the HCPCS code is inappropriate.

HCPCS	Description
J3399	Injection, onasemnogene abeparvovec-xioi, per treatment, up to 5x10^15 vector genomes (vg)

ICD-10	Description
G12.0	Infantile spinal muscular atrophy, type 1 (Werdnig-Hoffman)
G12.1	Other inherited spinal muscular atrophy (SMA) • Adult form SMA • Childhood form, type 2 SMA • Distal SMA • Juvenile form, type 3 SMA (Kugelberg-Welander) • Progressive bulbar palsy of childhood (Fazio-Londe) • Scapuloperoneal form SMA
G12.8	Other spinal muscular atrophies and related syndromes
G12.9	Spinal muscular atrophy, unspecified

ZOLGENSMA Kit Sizes		Indicated for	# of Vials		Total Vials	Units
NDC Number	Labeler	Patient Weight	5.5 mL [a]	8.3 mL [b]	per Kit	per Kit
71894-0120-02	Novartis Gene Therapies, Inc. (71894)	2.6 – 3.0 kg	0	2	2	1
71894-0121-03	Novartis Gene Therapies, Inc. (71894)	3.1 – 3.5 kg	2	1	3	1
71894-0122-03	Novartis Gene Therapies, Inc. (71894)	3.6 – 4.0 kg	1	2	3	1
71894-0123-03	Novartis Gene Therapies, Inc. (71894)	4.1 – 4.5 kg	0	3	3	1
71894-0124-04	Novartis Gene Therapies, Inc. (71894)	4.6 – 5.0 kg	2	2	4	1
71894-0125-04	Novartis Gene Therapies, Inc. (71894)	5.1 – 5.5 kg	1	3	4	1
71894-0126-04	Novartis Gene Therapies, Inc. (71894)	5.6 – 6.0 kg	0	4	4	1
71894-0127-05	Novartis Gene Therapies, Inc. (71894)	6.1 – 6.5 kg	2	3	5	1
71894-0128-05	Novartis Gene Therapies, Inc. (71894)	6.6 – 7.0 kg	1	4	5	1
71894-0129-05	Novartis Gene Therapies, Inc. (71894)	7.1 – 7.5 kg	0	5	5	1
71894-0130-06	Novartis Gene Therapies, Inc. (71894)	7.6 – 8.0 kg	2	4	6	1
71894-0131-06	Novartis Gene Therapies, Inc. (71894)	8.1 – 8.5 kg	1	5	6	1
71894-0132-06	Novartis Gene Therapies, Inc. (71894)	8.6 – 9.0 kg	0	6	6	1
71894-0133-07	Novartis Gene Therapies, Inc. (71894)	9.1 – 9.5 kg	2	5	7	1
71894-0134-07	Novartis Gene Therapies, Inc. (71894)	9.6 – 10.0 kg	1	6	7	1
71894-0135-07	Novartis Gene Therapies, Inc. (71894)	10.1 – 10.5 kg	0	7	7	1
71894-0136-08	Novartis Gene Therapies, Inc. (71894)	10.6 – 11.0 kg	2	6	8	1
71894-0137-08	Novartis Gene Therapies, Inc. (71894)	11.1 – 11.5 kg	1	7	8	1
71894-0138-08	Novartis Gene Therapies, Inc. (71894)	11.6 – 12.0 kg	0	8	8	1
71894-0139-09	Novartis Gene Therapies, Inc. (71894)	12.1 – 12.5 kg	2	7	9	1
71894-0140-09	Novartis Gene Therapies, Inc. (71894)	12.6 – 13.0 kg	1	8	9	1
71894-0141-09	Novartis Gene Therapies, Inc. (71894)	13.1 – 13.5 kg	0	9	9	1
71894-0142-10	Novartis Gene Therapies, Inc. (71894)	13.6 – 14.0 kg	2	8	10	1
71894-0143-10	Novartis Gene Therapies, Inc. (71894)	14.1 – 14.5 kg	1	9	10	1
71894-0144-10	Novartis Gene Therapies, Inc. (71894)	14.6 – 15.0 kg	0	10	10	1
71894-0145-11	Novartis Gene Therapies, Inc. (71894)	15.1 – 15.5 kg	2	9	11	1
71894-0146-11	Novartis Gene Therapies, Inc. (71894)	15.6 – 16.0 kg	1	10	11	1
71894-0147-11	Novartis Gene Therapies, Inc. (71894)	16.1 – 16.5 kg	0	11	11	1
71894-0148-12	Novartis Gene Therapies, Inc. (71894)	16.6 – 17.0 kg	2	10	12	1
71894-0149-12	Novartis Gene Therapies, Inc. (71894)	17.1 – 17.5 kg	1	11	12	1
71894-0150-12	Novartis Gene Therapies, Inc. (71894)	17.6 – 18.0 kg	0	12	12	1
71894-0151-13	Novartis Gene Therapies, Inc. (71894)	18.1 – 18.5 kg	2	11	13	1
71894-0152-13	Novartis Gene Therapies, Inc. (71894)	18.6 – 19.0 kg	1	12	13	1
71894-0153-13	Novartis Gene Therapies, Inc. (71894)	19.1 – 19.5 kg	0	13	13	1
71894-0154-14	Novartis Gene Therapies, Inc. (71894)	19.6 – 20.0 kg	2	12	14	1
71894-0155-14	Novartis Gene Therapies, Inc. (71894)	20.1 – 20.5 kg	1	13	14	1
71894-0156-14	Novartis Gene Therapies, Inc. (71894)	20.6 – 21.0 kg	0	14	14	1

[a] Vial nominal concentration is 2.0 x 10^{13} vg/mL and contains an extractable volume of not less than 5.5 mL.

[b] Vial nominal concentration is 2.0 x 10^{13} vg/mL and contains an extractable volume of not less than 8.3 mL.

Compliance

1. Should conflict exist between this policy and applicable statute, the applicable statute shall supersede.
2. Federal and State law, as well as contract language, including definitions and specific contract provisions or exclusions, take precedence over medical policy and must be considered first in determining eligibility for coverage.
3. Medical technology is constantly evolving, and Iowa Medicaid reserves the right to review and update medical policy on an annual or as-needed basis.

Medical necessity guidelines have been developed for determining coverage for member benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. Medical necessity guidelines are developed for selected physician-administered medications found to be safe and proven to be effective in a limited, defined population or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. Criteria are revised and updated annually, or more frequently if new evidence becomes available that suggests needed revisions.

References

[1] Zolgensma prescribing information (10/2023). Novartis Gene Therapies, Inc.: Bannockburn, IL. Available online at www.zolgensma-hcp.com. Accessed December 17, 2023.

[2] Blaschek A, Kölbel H, et al. Newborn Screening for SMA - Can a Wait-and-See Strategy be Responsibly Justified in Patients With Four SMN2 Copies? J Neuromuscul Dis. 2022;9(5):597-605. PMID: 35848034.

[3] Keinath MD, Prior DE, Prior TW. Spinal Muscle Atrophy: Mutations, Testing, and Clinical Relevance. Appl Clin Genet. 2021 Jan 25;14:11-25. PMID: 33531827.

[4] Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle Nerve. 2015 Feb;51(2):157-67. Epub 2014 Dec 16. PMID: 25346245.

[5] Calucho M, Bernal S, 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 Mar;28(3):208-215. Epub 2018 Jan 11. PMID: 29433793.

[6] See Keinath 2021, above.

[7] Cure SMA is a nonprofit organization that advocates for people with SMA and provides support services. It holds an annual conference that brings together researchers, doctors, people with SMA, and families. www.curesma.org.

[8] Glascock J, Sampson J, Haidet-Phillips A, Connolly A, Darras B, Day J, Finkel R, Howell RR, Klinger K, Kuntz N, Prior T, Shieh PB, Crawford TO, Kerr D, Jarecki J. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. J Neuromuscul Dis. 2018;5(2):145-158. PMID: 29614695.

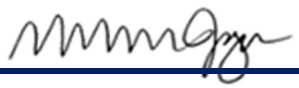
[9] Glascock J, Sampson J, et al. Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2. J Neuromuscul Dis. 2020;7(2):97-100. PMID: 32007960.

Development of utilization management criteria may also involve research into other state Medicaid programs, other payer policies, consultation with experts and review by the Medicaid Clinical Advisory Committee (CAC). These sources may not be referenced individually unless they are specifically published and are otherwise applicable to the criteria at issue.

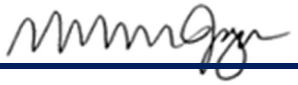
Criteria Change History

Change Date	Changed By	Description of Change	Version
[mm/dd/yyyy]			
Signature			

Change Date	Changed By	Description of Change	Version
[mm/dd/yyyy]			
Signature			

Change Date	Changed By	Description of Change	Version
01/19/2024	CAC	Annual review. Added new boxed warning information regarding serious liver injury and acute liver failure. Changed effective date from 04/21/2017 to 01/01/2021 to align with code info in MMIS. Changed approval date from 04/03/2019 to 10/16/2020 to align with Criteria Change History table. Updated Coding and Product Information section to include full list of Zolgensma kit sizes. Updated labeler to Novartis Gene Therapies (71894).	4
Signature William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
01/20/2023	CAC	Added criteria requiring documentation of 4 or less copies of *survival motor neuron 2 (SMN2)*. Incorporated paragraph with investigational uses of Zolgensma® into the criteria. Added requirement that risdiplam (Evrysdi®, a new SMA therapy FDA-approved since the previous version of this policy) would not be administered in conjunction with Zolgensma®. Added criteria requiring the full-term gestational age must be reached. if used in a neonatal patient born prematurely. Updated Descriptive Narrative.	3
Signature William (Bill) Jagiello, DO			

Criteria Change History *(continued)*

Change Date	Changed By	Description of Change	Version
07/16/2021	CAC	Added overview. Revised Descriptive Narrative. Added Guidelines, Coding, and Compliance sections. Updated References. Formatting changes.	2
Signature William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
10/16/2020	CAC	Criteria implementation.	1
Signature William (Bill) Jagiello, DO			

CAC = Medicaid Clinical Advisory Committee