Clinical Policy: Onasemnogene Abeparvovec (Zolgensma)

Reference Number: IL.PHAR.421
Effective Date: 10.08.20
Last Review Date: 4.15.23
Line of Business: Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Onasemnogene abeparvovec (Zolgensma®) is an adeno-associated virus (AAV) vector-based gene therapy.

FDA Approved Indication(s)

Zolgensma is indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in survival motor neuron 1 (SMN1) gene.

Limitation(s) of use:

- The safety and effectiveness of repeat administration of Zolgensma have not been evaluated.
- The use of Zolgensma in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Zolgensma is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Spinal Muscular Atrophy (must meet all)**:**

**Only for initial treatment dose; subsequent doses will not be covered.*

1. Diagnosis of spinal muscular atropy (SMA) confirmed with documentation of bi-allelic mutation in the SMN1 gene
2. Age ≤ 2 years;
3. Member has reached full-term gestational age
4. Prescribed by board certified in one of the following pediatric specialties or subspecialties: neurology, pulmonology, orthopedics, neonatal-perinatal medicine, clinical genetics and genomics, physical medicine and rehabilitation, neuromuscular medicine, or neurodevelopmental disabilities.
5. Documentation of both of the following (a and b):
   a. Baseline laboratory tests demonstrating Anti-AAV9 antibody titers ≤ 1:50 as determined by ELISA binding immunoassay;
   b. Baseline liver function test (AST, ALT, total bilirubin, prothrombin time, platelet count, and troponin-I levels within 30 days of request;

6. Member does not have advanced SMA (e.g., complete paralysis of limbs, ventilator dependence for 16 or more hours per day, tracheostomy, or non-invasive ventilation beyond the use for sleep; *see Appendix D*);
7. Member has not been previously treated with Zolgensma;
8. Zolgensma is not prescribed concurrently with Spinraza®; current Spinraza authorization will be discontinued upon Zolgensma approval.
9. Member does not have presence of prodrome or an active viral infection (*see Appendix D*);
10. Prescriber verifies member vaccine schedule has been reviewed and modified, if necessary.
11. Systemic corticosteroids equivalent to oral prednisolone dosed at 1mg/kg per day will be initiated one day prior to infusion for a total of 30 days and continued or tapered per prescribing information based on liver function.
12. After 30 days of required systemic-corticosteroid treatment, prescriber provides clinical update including AST, ALT, total bilirubin levels, prothrombin time, platelet count, and troponin I levels.

Approval duration: 4 weeks (one time infusion per lifetime)

B. Other diagnoses/indications (must meet 1 or 2):
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Spinal Muscular Atrophy
1. Re-authorization is not permitted.

Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.PMN.53 for Medicaid or evidence of coverage documents;
B. Advanced SMA.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ELISA: enzyme-linked immunosorbent assay
FDA: Food and Drug Administration
SMA: spinal muscular atrophy
SMN: survival motor neuron

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): acute serious liver injury and elevated aminotransferases

Appendix D: General Information

- SMA is an autosomal recessive genetic disorder. It is caused by mutations in the SMN1 (survival motor neuron) gene that is found on chromosome 5 (hence the name 5q-SMA). To develop SMA, an individual must inherit two faulty (deletion or mutation) SMN1 genes, one from each parent.
- There are other types of SMA that are not related to chromosome 5 or SMN. Safety and efficacy of Zolgensma in non-SMN-related SMA have not been established.
- SMN-related SMA is classified as type 1 through 4 depending on time of onset. The age of disease onset of symptoms correlates with disease severity: the earlier the age of onset, the greater the impact on motor function. Children who display symptoms at birth or in infancy typically have the lowest level of functioning (type 1). SMA onset in children (types 2 and 3), teens or adults (type 4) generally correlates with increasingly higher levels of motor function.
- SMN2 gene copy and SMA types
  - SMN2 gene copy numbers are variable in individuals with spinal muscular atrophy. Higher numbers typically correlate with less severe disease.
  - More than 95% of individuals with spinal muscular atrophy retain at least 1 copy of the SMN2 gene
  - About 80% of individuals with Type I spinal muscular atrophy have 1 or 2 copies of the SMN2 gene

  - About 82% of individuals with Type II spinal muscular atrophy have 3 copies of the SMN2 gene
  - About 96% of individuals with Type III spinal muscular atrophy have 3 or 4 copies of the SMN2 gene
- SMA Type I: onset of symptoms (e.g., hypotonia, muscle weakness, weak cry, lack of reflexes, difficulty swallowing, poor head control, round shoulder posture, inability to sit without support, tongue fasciculations, pooling secretions, poor suck and swallow reflexes, increased risk of aspiration, and failure to thrive) prior to the age of 6 months.
- Advanced SMA: complete paralysis of limbs, permanent ventilator dependence
- Permanent Ventilation: 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.
- Active infections include HIV, HBC, HCV, Zika, upper or lower respiratory tract infection, non-respiratory tract infection within 2 weeks of administration.
- The CHOP-INTEND score is a validated 16-item, 64-point scale shown to be reliable and sensitive to change over time for SMA Type 1. In a prospective cohort study of SMA type I patients (n = 34), the mean rate of decline in the CHOP-INTEND score was 1.27 points/year (95% CI 0.21-2.33, p = 0.02). A CHOP-INTEND score greater than 40 is considered a clinically meaningful change.
- The HINE Section 2 motor milestone exam is an easily performed and relatively brief standardized clinical neurological examination that is optimal for infants aged between 2 and 24 months with good inter-observer reliability. This endpoint evaluates seven different areas of motor milestone development, with a maximum score between 2-4 points for each, depending on the milestone, and a total maximum score of 26 points.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
SMA	Administer Zolgensma as a single-dose IV infusion over 60 minutes at the dose of 1.1×10^{14} vg/kg. One day prior to Zolgensma infusion, begin administration of systemic corticosteroids equivalent to oral prednisolone at 1mg/kg/day for a total of 30 days. Afterwards, evaluate liver function. No liver abnormalities, taper corticosteroids over the next 28 days. If liver abnormalities persist, continue systemic corticosteroids until resolution then taper over the next 28 days.	Once

VI. Product Availability

Zolgensma is shipped frozen in 10 mL vials with either 5.5 mL or 8.3 mL fill volumes. Each vial has a nominal concentration is 2.0×10^{13} vg/mL.

The customized kits come in differing vial quantities based on the patient's weight in kilograms as reflected within the package insert.

VII. References

1. Zolgensma Prescribing Information. Bannockburn, IL: Novartis Gene Therapies, Inc.; August 2022. Available at: https://www.novartis.com/us-en/sites/novartis_us/files/zolgensma.pdf. Accessed February 2, 2023.
2. Mendell JR, Al-zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *N Engl J Med*. 2017;377(18):1713-1722.
3. Institute for Clinical and Economic Review (ICER). Final Evidence Report – Spinraza and Zolgensma for spinal muscular atrophy: effectiveness and value. Available at: https://icer.org/wp-content/uploads/2020/10/ICER_SMA_Final_Evidence_Report_110220.pdf. Accessed February 7, 2023.
4. Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord*. 2018;28(2):103-115.
5. Finkel RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord*. 2018;28(3):197-207.
6. Cobben JM, de Visser M, Scheffer H, et al. Confirmation of clinical diagnosis in requests for prenatal prediction of SMA type I. *J Neurol Neurosurg Psychiatry.* 1993; 56: 319-21.
7. Maitre NL, Chorna O, Romeo DM, and Guzzetta A. Implementation of the Hammersmith Infant Neurological Examination in a High-Risk Infant Follow-Up Program. *Pediatric Neurology*. 2016; 65:31-38.
8. Darras BT, Royden Jones H Jr, Ryan MM, et al. Neuromuscular Disorders of Infancy, Childhood, and Adolescence: A Clinician's Approach. 2nd ed. London, UK: Elsevier; 2015.
9. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology*. 2014; 83: 810-7.
10. De Sanctis R, Coratti G, Pasternak A, et al. Developmental milestones in type I spinal muscular atrophy. *Neuromuscul Disord*. 2016; 26: 754-9.
11. SMA Foundation. About SMA: Informational Resources. SMA Overview. Website: Available at: http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf. Accessed 5.09.19
12. New AveXis data at AAN showed long-term durability of Zolgensma in patients with spinal muscular atrophy (SMA) Type 1; Novartis Web site; https://www.novartis.com/news/media-releases/new-avexis-data-aan-showed-long-term-durability-zolgensma-patients-spinal-muscular-atrophy-sma-type-1; Published May 7, 2019. Access May 9, 2019.
13. AveXis data reinforce effectiveness of Zolgensma in treating spinal muscular atrophy (SMA) Type 1; Novartis Web site; https://www.novartis.com/news/media-releases/avexis-data-reinforce-effectiveness-zolgensma-treating-spinal-muscular-atrophy-sma-type-1; Published April 16, 2019. Access May 9, 2019.
14. AveXis presented robust data at AAN demonstrating efficacy of Zolgensma in broad spectrum of spinal muscular atrphy (SMA) patients; Novartis Web site; https://www.novartis.com/news/media-releases/avexis-presented-robust-data-aan-demonstrating-efficacy-zolgensma-broad-spectrum-spinal-muscular-atrophy-sma-patients; Published May 5, 2019. Accessed May 9, 2019.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	06.11.19	08.19
2Q 2020 annual review: no significant changes; clarified advanced SMA definition in initial approval criteria regarding permanent ventilation dependence; clarified that clinical deterioration from Spinraza should be upon all loading doses have been completed; references reviewed and updated.	04.28.20	05.20
Updated criteria language to restrict concomitant use with Evrysdi and require evidence of clinical deterioriation prior to switching; references reviewed and updated.	08.25.20	08.20
Policy created, adapted from CP.PHAR.421 **Onasemnogene Abeparvovec (Zolgensma)** for migration to HFS PDL. **Removed**: If the member is currently on Evrysdi, must meet the following (a and b): a. Provider must submit evidence of clinical deterioration (e.g., sustained decrease in CHOP-INTEND score over a period of 3 to 6 months); b. Documentation of provider attestation of clinical deterioration and Evrysdi discontinuation; 2. Documentation of one of the following baseline scores (*see Appendix D*) (a or b):	10.08.20	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
a. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder (CHOP-INTEND) score; b. Hammersmith Infant Neurological Examination (HINE) Section 2 motor milestone score; 3. Genetic testing confirming 1, 2, or 3 copies of SMN2 gene; 4. Genetic testing confirms the presence of one of the following (a, b, or c): a. Homozygous deletions of SMN1 gene (e.g., absence of the SMN1 gene); b. Homozygous mutation in the SMN1 gene (e.g., biallelic mutations of exon 7); c. Compound heterozygous mutation in the SMN1 gene (e.g., deletion of SMN1 exon 7 (allele 1) and mutation of SMN1 (allele 2)); 5. Total dose does not exceed 1.1 x 10^{14} vector genomes (vg) per kilogram (kg). 6. If the member is currently on Spinraza, must meet the following (a and b): a. Provider must submit evidence of clinical deterioration (e.g., sustained decrease in CHOP-INTEND score over a period of 3 to 6 months) upon completion of all loading doses of Spinraza; b. Documentation of provider attestation of clinical deterioration and Spinraza discontinuation; Added: 7. Member has reached full-term gestational age 8. Prescribed by board certified in one of the following pediatric specialties or subspecialties: neurology, pulmonology, orthopedics, neonatal-perinatal medicine, clinical genetics and genomics, physical medicine and rehabilitation, neuromuscular medicine, or neurodevelopmental disabilities.		

Reviews, Revisions, and Approvals	Date	P&T Approval Date
9. Prescriber verifies member vaccine schedule has been reviewed and modified, if necessary. 10. Systemic corticosteroids equivalent to oral prednisolone dosed at 1mg/kg per day will be initiated one day prior to infusion for a total of 30 days and continued or tapered per prescribing information based on liver function. 11. After 30 days of required systemic-corticosteroid treatment, prescriber provides clinical update including AST, ALT, total bilirubin levels, prothrombin time, platelet count, and troponin I levels.		
3Q 2021 Annual Review References reviwed and updated	7.2.21	
2Q 2023 annual review: no significant changes; template changes applied to other diagnoses/indications, HCPS code added, references reviewed and updated.	4.15.23	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to

applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.