Clinical Policy: Onasemnogene Abeparvovec (Zolgensma, Itvisma)

Reference Number: PA.CP.PHAR.421
Effective Date: 01/2020
Last Review Date: 01/2026

Description
Onasemnogene abeparvovec (Zolgensma®, Itvisma®) 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.

Itvisma is indicated for the treatment of SMA in adult and pediatric patients 2 years of age and older with confirmed mutation in SMN1 gene.

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 PA Health & Wellness® that Zolgensma and Itvisma are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria
A. Spinal Muscular Atrophy (must meet all)**:**
1. Diagnosis of SMA;
2. 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));
3. Prescribed by or in consultation with a neurologist;
4. Member meets one of the following (a or b):
   a. If request is for **Zolgensma**, then both of the following (i and ii):
      i. Age < 2 years;
      ii. Documentation of one of the following baseline scores (*see Appendix D*) (1 or 2):
         1. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder (CHOP-INTEND) score;

2. Hammersmith Infant Neurological Examination (HINE) Section 2 motor milestone score;

b. If request is for **Itvisma**, then all of the following (i and ii):
   i. Age 2 years or older;
   ii. Documentation of one of the following baseline scores (1, 2, 3, 4, or 5; *see Appendix D*):
      1. Hammersmith functional motor scale expanded (HFMSE) score;
      2. Revised Hammersmith Scale (RHS);
      3. Upper Limb Module (ULM)
      4. Revised Upper Limb Module (RULM);
      5. 6-Minute Walk Test (6MWT);

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 (i.e., alanine aminotransferase, total bilirubin, gamma-glutamyl transferase or glutamate dehydrogenase), platelet counts, and troponin-I less than the upper limit of normal;
6. Member does not have advanced SMA as defined by one of the following (a or b):
   a. **If age <2 years**, member does not have complete paralysis of limbs, permanent ventilator dependence, tracheostomy (*see Appendix D*);
   b. **If age > 2 years**, member does not have complete paralysis of limbs, permanent ventilator dependence, tracheostomy;
7. Member has not been previously treated with Zolgensma or Itvisma;
8. Zolgensma or Itvisma is not prescribed concurrently with Spinraza or Everysdi;
9. If the member is currently on Spinraza or Evrysdi, one of the following (a, b or c):
   a. Request is for Zolgensma, and Spinraza or Evrysdi is being used as a bridge therapy (i.e., a strategy where members receive temporary treatments like Spinraza or Evrysdi to stabilize their condition while awaiting a one-time IV gene therapy for SMA Type 1);*
      **Bridging therapy does not apply to Itvisma.*
   b. Clinically significant adverse effects are experienced;
   c. Both of the following (i and ii):
      i. Provider must submit evidence of clinical deterioration (e.g., sustained decrease in CHOP-INTEND or HFMSE score over a period of at least 6 months) upon completion of all loading doses of Spinraza/Evrysdi;
      ii. Documentation of provider attestation of clinical deterioration and Spinraza/Evrysdi discontinuation;
10. Total dose does not exceed a single infusion of one of the following (a or b):
    a. Zolgensma: 1.1×10^{14} vector genomes (vg) per kilogram (kg);
    b. Itvisma: 1.2×10^{14} vg.

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

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Spinal Muscular Atrophy

1. Continued therapy will not be authorized as Zolgensma and Itvisma are indicated to be dosed one time only.
   Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2):

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

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 – PA.CP.PMN.53;
B. Advanced SMA;
C. SMA Type 4.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ELISA: enzyme-linked immunosorbent assay
FDA: Food and Drug Administration
HFMSE: Hammersmith functional motor scale expanded
RHS: Revised Hammersmith scale
RULM: Revised upper limb module
SMA: spinal muscular atrophy
SMN: survival motor neuron
ULM: upper limb module
6MWT: 6-minute walk test

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): serious liver injury (*Zolgensma, Itvisma*) and acute liver failure (*Zolgensma only*)

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/Itvisma 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.The HFSME score combines the Hammersmith Functional Motor Scale with a 13-item expansion module for ability to distinguish motor skills among individuals who may be older or with SMA types II and III. Each item is graded from 0 to 3, with 0 signifying no response, with a total of 66 points. HFMSE has demonstrated reliability and validity in patients with SMA. An increase of greater than 2 points in total score is unlikely in untreated SMA.
- The RHS is an ordinal scale which consist of 33 items with grades of 0,1 and 2. For individuals who can achieve the task without any compensation it is given a score of 2. For those who only attempt the movement or finish it with some form of compensation is scored 1 and sore of 0 is given when patients are unable to perform any part of the item. The total maximum score is 69 points.

- The RULM is a set of 19 tasks that measure motor function in non-ambulatory SMA patients. Each task is assessed with a 3-point ordinal scale, with a total maximum score of 37 points. Meanwhile, the maximum score for ULM was 18.
- The 6MWT is a clinical outcome measure for ambulatory SMA that has been determined to be functionally meaningful and capable of capturing disease severity.

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Onasemnogene abeparvovec-xioi (Zolgensma)	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 1 mg/kg/day for at least a total of 30 days. Afterwards, evaluate liver function. If 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. If liver function abnormalities continue to persist $\geq 2 \times$ ULN after the 30-day period of systemic corticosteroids, promptly consult a pediatric gastroenterologist or hepatologist	One dose per lifetime
Onasemnogene abeparvovec-brve (Itvisma)	Administer Itvisma as an intrathecal bolus injection over approximately 1 to 2 minutes through the lumbar puncture needle at the dose of 1.2×10^{14} vg. One day prior to Itvisma infusion, begin administration of systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg/day for at least a total of 30 days. Afterwards, evaluate liver function. If 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. If at any time patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone, based on the patient's clinical course, prompt consultation with a gastroenterologist or hepatologist and adjustment	One dose per lifetime

Drug Name	Dosing Regimen	Maximum Dose
	to the recommended corticosteroid regimen may be considered.	

VI. Product Availability

Drug Name	Availability
Onasemnogene abeparvovec-xioi (Zolgensma)	• 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 x 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.
Onasemnogene abeparvovec-brve (Itvisma)	Single dose vial: 1.2 x 10^{14} vg of onasemnogene abeparvovec in 3 mL of suspension

VII. References

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15. Schroth M, Deans J, Arya K, et al. Spinal muscular atrophy update in best practices: recommendations for diagnosis considerations. Neurol Clin Pract. 2024 Aug;14(4):e200310. doi: 10.1212/CPJ.0000000000200310.

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 (Zolgensma)

Reviews, Revisions, and Approvals	Date
Policy created	01/2020
1Q 2021 annual review: updated criteria language to restrict concomitant use with Evrysdi; references reviewed and updated.	01/2021
1Q 2022 annual review: references reviewed and updated.	01/2022
2Q 2023 annual review: no significant changes; HCPCS Code added; references reviewed and updated.	04/2023
2Q 2024 annual review: no significant changes; updated boxed warnings description to "serious liver injury and acute liver failure" to align with prescriber information; references reviewed and updated.	04/2024
2Q 2025 annual review: for initial approval criteria, added option of "four copies of SMN2 gene, determined by a quantitative assay that is able to distinguish between four SMN2 gene copies and five or more SMN2 gene copies" as supported by practice guidelines; references reviewed and updated.	04/2025
RT4: added newly approved dosage form, Itvisma, with the following revisions: added documentation for inability to walk independently per study protocol; defined advanced SMA for 2 years and older; added SMA type 4 in section III; required 2 or 3 SMN2 copies. Updated language under Policy/Criteria to effectively redirect prior authorization reviews to Precision Drug Action Committee (PDAC) Utilization Management Review.	01/2026