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## Subject: Onasemnogene abeparvovec (Zolgensma)

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### DESCRIPTION:

Spinal muscular atrophy (SMA) is a group of genetic disorders characterized by a loss of motor neurons. While there are numerous gene mutations that can cause the different forms of SMA, 95% of cases result from a homozygous deletion or mutation in the 5q13 survival of motor neuron (SMN1) gene. This deficiency results in degeneration of motor neurons causing muscle atrophy, particularly in the limbs and the muscles that control the mouth, throat and respiration. A second gene, SMN2, is nearly identical to SMN1 but does not produce much functional (i.e., full length, stable) SMN protein. While there is generally one SMN1 per chromosome, there is a variable number of SMN2 gene copies.

The severity of SMA (an autosomal recessive disorder) is highly variable and correlates mainly with the number of SMN2 gene copies. The clinical features can be classified based on the age of onset and maximum motor function (table 1).

Table 1. SMA Classification

Type	Age of onset	Highest Function	Natural Age of Death	Copies of SMN2
0	Prenatal	Respiratory failure	< 1 month	1
I (Werdnig-Hoffman disease)	0-6 months	Never sit	< 2 years	2
II (Dubowitz disease)	< 18 months	Never stand	> 2 years	3, 4
III (Kugelberg-Welander disease)	18 months-21 years	Stand or ambulatory	Adult	3, 4
IV (adult onset)	> 21 years	Ambulatory	Adult	4-8

The incidence of SMA is approximately 1 in 11,000 live births and it is reported to be the leading genetic cause of infant death. Carrier frequencies are estimated at 1 in 40 to 1 in 60. SMA can be diagnosed by DNA analysis detection of SMN1 deletion in both SMN1 alleles. This is approximately 95% sensitive (100% specific) for patients with clinical features suspicious for SMA.

The first FDA approved therapy for treatment of SMA was nusinersen (Sprinraza), an antisense oligonucleotide. It is administered as an intrathecal infusion every 4 months. Zolgensma (onasemnogene abeparvovec-xioi), an adeno-associated virus vector-based gene therapy, was approved in May 2019 for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene. It is administered as a single, one-time infusion that works by inducing SMN expression in motor neurons and peripheral tissues. The safety and efficacy of repeat administration has not been evaluated, nor has use in patient with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator-dependence). The safety and efficacy of Zolgensma were evaluated in a phase 1, open-label study (NCT02122952) of individuals with type 1 SMA confirmed by genetic testing (n=15). Participants were included if they were less than 9 months of age, had 2 copies of SMN2, and developed symptoms (hypotonia by clinical evaluation with delay in motor skills, poor head control, round shoulder posture and hypermobility of joints) of SMA prior to 6 months of age. Those who required invasive ventilator support or may be put on non-invasive ventilator support (BiPAP) for less than 16 hours a day were excluded. Participants were enrolled in two cohorts based on the dose of Zolgensma. Cohort 1 (low dose, n=3) received a  $6.7 \times 10^{13}$  vg/kg dose, while cohort 2 (high dose, n=12) received a  $2.0 \times 10^{14}$  vg/kg dose.

The primary outcome was safety (treatment-related adverse event of grade 3 or higher), with a secondary outcome of time until death or permanent ventilation. As of a data cut-off date of August 7, 2017, all participants had reached an age of at least 20 months and did not require permanent mechanical ventilation; the median age at their last pulmonary assessment was 30.8 months in cohort 1 and 25.7 months in cohort 2. In contrast, only 8% of patients in a historical cohort did not require ventilation at this same age. All the participants in cohorts 1 and 2 had increased scores from baseline on the CHOP INTEND scale and maintained these changes during the study. Those in cohort 2 had mean increases of 9.8 points at 1 month and 15.4 points at 3 months ( $P < 0.001$  for both comparisons); while 11 attained and sustained scores of more than 40 points. At the study cutoff on August 7, 2017, cohort 1 had a mean increase of 7.7 points from a mean baseline of 16.3 points, and cohort 2 had a mean increase of 24.6 points from a mean baseline of 28.2 points.

As of August 7, 2017, a total of 56 serious adverse events were observed in 13 participants. Of these events, 2 events were treatment-related grade 4 events on the basis of laboratory values. Patient 1 in cohort 1 had elevations in serum aminotransferase levels (31 times the upper limit of the normal range for ALT and 14 times the upper limit for AST. Treatment prior to and after infusion was subsequently administered in the remaining participants. Of the 241 nonserious adverse events, 3 were deemed to be treatment-related and consisted of asymptomatic elevations in serum aminotransferase levels in 2 patients (ALT and AST, both less than 10 times the upper limit of the normal range), which were resolved without additional prednisolone treatment. There were no other abnormalities on liver-function testing.

## **POSITION STATEMENT:**

Onasemnogene abeparvovec (Zolgensma) **meets the definition of medical necessity** when all of the following criteria are met:

1. Indication for use is spinal muscular atrophy (SMA)
2. Member's diagnosis has been confirmed by either of the following:

- a. Homozygous deletion of SMN1 gene exon 7 (with or without deletion of exon 8) – laboratory documentation must be provided
  - b. Single copy of SMN1 with sequencing of the coding region to confirm a mutation rendering a homozygous dysfunction of the gene – laboratory documentation must be provided
3. Member has 4 or fewer copies of the SMN2 gene – laboratory documentation must be provided
  4. Member's pre-treatment anti-AAV9 antibody titer is less than or equal to 1:50
  5. Member's pre-treatment liver function has been assessed by clinical examination and laboratory testing and will be monitored for at least 3 months after infusion
  6. Member is not dependent on invasive ventilation (tracheostomy)
  7. Member is not dependent on respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in absence of an acute reversible illness, excluding perioperative ventilation
  8. Member does not have complete paralysis of limbs
  9. Treatment is prescribed by or in consultation with a board certified (or board eligible) neurologist
  10. Member has not previously received gene therapy (including Zolgensma) for SMA
  11. Member is not concurrently enrolled in a clinical trial to receive an experimental therapy for SMA
  12. Member will not receive treatment with nusinersen (Spinraza) or risdiplam (Evrysdi)  
**NOTE:** Member's medical record will be reviewed and any current authorizations for nusinersen or risdiplam will be terminated upon Zolgensma approval
  13. Member will receive systemic corticosteroids before and after infusion
  14. Dose does not exceed  $1.1 \times 10^{14}$  vector genomes (vg) per kg of body weight
  15. Member is less than 2 years of age

**Approval duration:** 6 months

**NOTE:** Approval is for 1 lifetime treatment of onasemnogene abeparvovec (Zolgensma). Provider agrees in good faith to share plan specific treatment outcome measures.

## **DOSAGE/ADMINISTRATION:**

**THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.**

### **FDA-approved**

- $1.1 \times 10^{14}$  vector genomes (vg) per kg of body weight
- Administer as an intravenous infusion over 60 minutes

### Dose Adjustments

- None

### Drug Availability

- Suspension for intravenous infusion, supplied as single-use vials.
- Provided in a kit containing 2 to 9 vials, as a combination of 2 vial fill volumes (either 5.5 mL or 8.3 mL). All vials have a nominal concentration of  $2.0 \times 10^{13}$  vector genomes (vg) per mL.
- Each vial contains an extractable volume of not less than either 5.5 mL or 8.3 mL.

## PRECAUTIONS:

### Boxed Warning

- Acute serious liver injury. Assess liver function of all patients by clinical examination and laboratory testing prior to infusion and for at least 3 months after infusion. Administer systemic corticosteroids before and after infusion.

### Contraindications

- None

### Precautions/Warnings

- Thrombocytopenia
- Elevated troponin-I

## BILLING/CODING INFORMATION:

### HCPCS Coding

J3399	Injection, onasemnogene abeparvovec-xioi, per treatment, up to $5 \times 10^{15}$ vector genomes
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### ICD-10 Diagnosis Codes That Support Medical Necessity

G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]
G12.1	Other inherited spinal muscular atrophy
G12.8	Other spinal muscular atrophies and related syndromes
G12.9	Spinal muscular atrophy, unspecified

## REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

## PROGRAM EXCEPTIONS:

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Part D:** Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

**Medicare Advantage:** No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

## DEFINITIONS:

None

## RELATED GUIDELINES:

None

## OTHER:

None

## REFERENCES:

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**COMMITTEE APPROVAL:**

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/10/24.

**GUIDELINE UPDATE INFORMATION:**

06/15/19	New Medical Coverage Guideline.
07/25/19	Revised guideline, consisting of Description, Position Statement, Dosage/Administration, Billing/Coding, Related Guidelines, Other, References
07/01/20	Revision: Added HCPCS code J3399 and deleted codes C9399 and J3590.
04/15/21	Review of guideline; Updated references, position statement
01/15/22	Review of guideline; Updated references
01/15/23	Review of guideline; Updated references.
01/15/24	Review of guideline; Updated references.
05/15/24	Revision of guideline; Updated position statement.