DR.005.A ZOLGENSMA ® (onasemnogene abeparvovec-xioi)

Health Partners Plans

Title: ZOLGENSMA ® (onasemnogene abeparvovec-xioi)
Policy #: DR.005.A
Type: Medical
Sub-Type: Drug (DR)

Original Implementation Date: 03/1/2020
Version Date [A]: 2/1/2020
Last Review Date: 1/15/2020
Notification Published: 30 Day

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FDA APPROVED INDICATIONS

Zolgensma® is an adeno-associated virus 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.

OFF-LABELED 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.

PRIOR AUTHORIZATION CRITERIA

INITIAL CRITERIA

1) Is the medication prescribed by or in consultation with a physician who specializes in the treatment of spinal muscular atrophy (SMA)? *If YES, go to 2. If NO, refer to Medical Director.*

2) Does the patient have a documented diagnosis of SMA with the following: genetically confirmed bi-allelic *SMN1* gene deletions or variants? *If YES, go to 3. If NO, refer to Medical Director.*

3) Does the patient have advanced SMA disease (complete limb paralysis, invasive ventilation support, etc.)? *If NO, go to 4. If YES, refer to Medical Director.*

4) Was the patient premature? *If NO, go to 6. If YES, go to 5.*

5) Will the Zolgensma infusion be delayed until the corresponding full-time gestational age is reached? *If YES, go to 6. If NO, refer to Medical Director.*

6) Is the patient less than 2 years of age? *If YES, go to 7. If NO, refer to Medical Director.*

7) Does the patient have a baseline anti-adeno-associated virus serotype 9 (AAV9) antibody titer ≤1:50 measured by enzyme-linked immunosorbent assay (ELISA)? *If YES, go to 8. If NO, refer to Medical Director.*

8) Will systemic corticosteroids be administered beginning one day prior to infusion for a total of 30 days? *If YES, go to 9. If NO, refer to Medical Director.*

9) Is there documentation for baseline liver function tests (AST, ALT, total bilirubin, and prothrombin time) and will they continue to be monitored for at least 3 months after the infusion or until results are unremarkable? *If YES, go to 10. If NO, refer to Medical Director.*

10) Is there documentation for baseline platelet count and troponin-I levels and will they continue to be monitored? *If YES, go to 11. If NO, refer to Medical Director.*

11) Is the dose prescribed within the FDA labeled dose of 1.1×10^{14} vector genomes per kilograms (vg/kg) of body weight? *If YES, approve for one time dose. If NO, refer to Medical Director.*

RENEWAL CRITERIA

Zolgensma is meant for a one-time-only dose. The safety and effectiveness of repeat administration of Zolgensma has not been evaluated.

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 the majority of the survival motor neuron (SMN) protein within the body, where as 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, Kugelberg-Welander 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.

DOSAGE AND ADMINISTRATION

Zolgensma is for single-dose intravenous infusion only:

- Recommended dosage: Zolgensma 1.1×10^{14} vector genomes (vg) per kg of body weight.
- Administer Zolgensma as an intravenous infusion over 60 minutes through a venous catheter.
- 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 2.0×10^{13} vector genomes (vg) per mL.
- Requires premedication with systemic corticosteroids.
- Equivalent to oral prednisolone at 1 mg/kg per day beginning 1 day prior to infusion for a total of 30 days
- Zolgensma is shipped frozen at ≤ -60 °C. Thaw prior to infusion. Store refrigerated. Must use within 14 days of receipt.

RISK FACTORS/SIDE EFFECTS

Most common adverse reactions (incidence ≥5%) noted in trials were elevated liver enzymes and vomiting.

Hepatic effects: acute serious liver injury and elevated aminotransferases were observed in clinical trials; assess liver function by clinical examination and laboratory testing. Administer systemic corticosteroids before and after Zolgensma infusion.

Thrombocytopenia: transient decreases in platelet count were observed at different time points through the trial after Zolgensma infusion. Monitor platelet counts before and periodically after Zolgensma infusion until return to baseline.

Cardiac effects: transient increases in cardiac troponin-I level were observed after Zolgensma infusion; clinical importance is unknown. However, cardiac toxicity was observed in animal studies. Monitor troponin-I before and periodically after Zolgensma infusion until return to baseline.

BLACK BOX WARNING

Acute serious liver injury and elevated aminotransferases can occur with Zolgensma.

- Patients with pre-existing liver impairment may be at higher risk.
- An assessment of liver function of all patients by examination and laboratory parameters must be performed prior to infusion.
- Liver enzymes (AST, ALT), total bilirubin and prothrombin time.
- Liver function must be monitored for at least 3 months after administration.

MONITORING

Efficacy:

- **Physical findings:**
  - Achievement of developmental milestones (e.g., kicking, head control, rolling, sitting, crawling, standing, walking) may indicate efficacy.

Toxicity:

- Laboratory parameters: obtain at baseline and then as directed below.
  - **Liver function:** (clinical exam, AST, ALT, total bilirubin, prothrombin time): weekly for the first month; then every other week for months 2 and 3, until results are unremarkable (normal clinical exam, total bilirubin, and prothrombin results, and ALT and AST levels below 2 × ULN).
  - **Platelet count**: weekly for the first month and then every other week for months 2 and 3 until platelet count returns to baseline.
  - **Troponin-I**: weekly for the first month and then monthly for months 2 and 3 until troponin-I level returns to baseline.

CODING

NOTE: *The Current Procedural Terminology (CPT®) codes and Healthcare Common Procedure Coding System (HCPCS) codes 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 Code	Description
N/A	

CPT® is a registered trademark of the American Medical Association.

HCPCS Code	Description
J3490	Unclassified drugs.

ICD-10 code	Description
G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffman].

POLICY HISTORY

Summary	Version	Version Effective Date
New Policy.	A	3/1/2020

REFERENCES

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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]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease.

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.

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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/Patient-Caregiver-Education/Fact-Sheets/Spinal-Muscular-Atrophy-Fact-Sheet.

6. Zolgensma ® [prescribing information]. AveXis Inc., Bannockburn, IL. 2019.