Zolgensma (onasemnogene abeparvovec-xioi) Clinical Coverage Criteria

Overview

Spinal muscular atrophy (SMA) with bi-allelic mutations in the SMN1 gene is a serious autosomal recessive neurodegenerative disorder. In approximately 96% of patients, SMA is caused by homozygous deletions of exons 7 and 8 of the SMN1 gene, or, in some cases, only of exon 7of the SMN1 gene on chromosome 5q13.2, whereas the remaining patients harbor compound heterozygous mutations, such as an SMN1 deletion in one allele and an intragenic mutation (insertions, deletions, or point mutations) in the other SMN1 allele (Mercuri et al., 2018).

Infantile SMA is the most severe and common form of SMA, with an estimated incidence of 1 in 10,000 live births and prevalence of about 1–2 per 100,000. Infants with SMA have problems with motor function, such as holding their head up, sucking and breathing that may be present at birth or by the age of 6 months. Most patients with infantile-onset SMA do not survive past early childhood due to respiratory failure. It is the most common monogenic cause of infant mortality.

On May 24, 2019, the U.S. Food and Drug Administration (FDA) approved Zolgensma (AveXis, Inc., Bannockburn, IL), 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. The vector delivers a fully functional copy of human SMN gene into the target motor neuron cells. A one-time intravenous administration of Zolgensma results in expression of the SMN protein in a child's motor neurons, which improves muscle movement and function, and survival of a child with SMA. Dosing is determined based on the weight of the patient.

The FDA approval of Zolgensma is based on safety and effectiveness data from a completed Phase 1 clinical trial involving 15 infants and an ongoing Phase 3 clinical trial involving 21 infants (NCT 02122952). Two doses were compared in the Phase 1 safety trial. Three patients were enrolled in the low-dose cohort and 12 patients were enrolled in the high-dose cohort. The mean age of patients at the time of treatment was 6.3 months (range 5.9 to 7.2 months) in the low-dose cohort and 3.4 months (range 0.9 to 7.9 months) in the high-dose cohort. Comparison of the results for survival at 24 months in the high-dose cohort to the results in the low-dose cohort support the effectiveness of Zolgensma. There was a clear dose-response relationship with respect to effectiveness in favor of the higher dose. No patients in this study died. One patient in the low-dose cohort required tracheostomy (i.e., permanent ventilation), and thus did not reach the survival efficacy endpoint. Of the 15 total subjects, 13 were reported to experience at least one serious adverse event: all 3 subjects in the low-dose cohort, and 10 of the 12 subjects in the high-dose cohort. The majority were pulmonary infections. Pulmonary infections are a common occurrence in the natural history of infantile-onset SMA. Any increased susceptibility to these SAEs due to Zolgensma. Two serious adverse events (elevated aminotransferases) were considered definitely related to treatment with Zolgensma.

The primary evidence of effectiveness is based on preliminary results from 21 patients treated with Zolgensma in an open-label, single-arm Phase 3 clinical trial (NCT 03306277). All patients in the treatment arm received the higher dose. Before treatment with Zolgensma, none of the 21 patients required non-invasive ventilatory support and all patients were able to exclusively feed orally (i.e., no need for non-oral nutrition). The mean age of patients at the time of treatment was

3.9 months (range 0.5 to 5.9 months). As of the March 2019 data cutoff, 19 patients were alive without the need for permanent ventilation (i.e., event-free survival) and continued in the trial; one patient withdrew from the study at age 11.9 months; and one patient died at age 7.8 months due to disease progression.

All patients enrolled in these two trials experienced onset of clinical symptoms consistent with SMA before 6 months of age. All patients had genetically confirmed bi-allelic SMN1 deletions and 2 copies of SMN2, and absence of the c.859G>C modification in exon 7 of SMN2 (which predicts a milder phenotype). All patients had baseline anti-AAV9 antibody titers of ≤ 1:50, measured by enzyme-linked immunosorbent assay (ELISA). Patients treated in both trials received a course of oral corticosteroid to suppress potential immune reactions to Zolgensma.

Patients enrolled in the Phase 1 study were invited to participate in a 15-year follow-up study (NCT 03421977). Thirteen of the original 15 patients enrolled, including 3 patients from the low-dose cohort and 10 from the therapeutic-dose cohort. Two families declined participation. At 5-years post treatment, all 10 patients in the therapeutic-dose cohort were alive and did not require permanent ventilation; all 3 of the patients in the low-dose cohort remain alive, and 2 of these 3 remain free of permanent ventilation. Serious adverse events were reported for 8 patients (62%). The most frequently reported SAEs were related to the underlying SMA disease process (Mendell et al., 2021).

Zolgensma has a black boxed warning that acute serious liver injury can occur. Patients with pre-existing liver impairment may be at higher risk of experiencing serious liver injury. Clinical examination and laboratory tests to assess liver function should be completed prior to treatment with Zolgensma, and patients' liver function should be monitored for at least three months after Zolgensma administration.

Policy

This Policy applies to the following Fallon Health products:

☒ Commercial

☒ Medicare Advantage

☒ MassHealth ACO

☒ NaviCare

☒ PACE

Fallon Health follows guidance from the Centers for Medicare and Medicaid Services (CMS) for organization (coverage) determinations for Medicare Advantage plan members. National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs) and guidance in the Medicare manuals are the basis for coverage determinations. When there is no NCD, LCD, LCA or manual guidance, Fallon Health Clinical Coverage Criteria are used for coverage determinations.

Medicare does not have an NCD for Zolgensma (onasemnogene abeparvovec-xioi). National Government Services does not have an LCD or LCA for Zolgensma (MCD search 06/22/2021).

For plan members enrolled in NaviCare and PACE plans, Fallon Health follows Medicare guidance for coverage determinations. When there is no Medicare guidance or if the plan member does not meet medical necessity criteria in Medicare guidance, Fallon Health Clinical Coverage Criteria are used for coverage determinations. Fallon Health's Clinical Coverage Criteria are developed in accordance with the definition of Medical Necessity in 130 CMR 450.204 and are therefore no more restrictive than MassHealth Medical Necessity Guidelines. In the event that neither Medicare nor Fallon Health have coverage criteria, Fallon Health will follow MassHealth Guidelines for Medical Necessity Determination (Fallon Health Weinberg PACE will follow New York State Medicaid Guidance). Each PACE plan member is assigned to an

Interdisciplinary Team. When there is no Medicare or State Medicaid Agency guidance, the PACE plan member's Interdisciplinary Team is responsible for coverage determinations.

For MassHealth ACO members, Fallon Health Clinical Coverage Criteria are used for coverage determinations. Fallon Health's Clinical Coverage Criteria are developed in accordance with the definition of Medical Necessity in 130 CMR 450.204 and are therefore no more restrictive than MassHealth Medical Necessity Guidelines.

Prior authorization is required for Zolgensma. This prior authorization is separate from any prior authorization that may be required for the member's inpatient or outpatient encounter. Submission of medical records documenting all of the medical necessity criteria is required on all requests for Zolgensma.

Zolgensma is considered medically necessary for the treatment of spinal muscle atrophy (SMA) when medical record documentation confirms all of the following criteria are met:

1. The member is less than 2 years of age on the date of Zolgensma infusion.
2. The prescriber is a neurologist with expertise in diagnosing and treating SMA.
3. Genetic testing confirms the presence of biallelic survival motor neuron 1 (SMN1) mutation (e.g. homozygous deletion or compound heterozygous mutation) and at least 2 copies but not more than 3 copies of the SMN2 gene.
4. Anti-adeno-associated virus serotype 9 (AAV9) antibody titer is </= 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay.
5. The member does not have evidence of advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence). Permanent ventilator dependence is defined as invasive ventilatory support (endotracheal tube or tracheostomy) or non-invasive respiratory assistance for 16 hours or more per day for 14 continuous day in the absence of an acute reversible illness).

The plan member may not receive concomitant survival motor neuron protein (SMN) modifying therapy (e.g., Spinraza, nusinersen). The plan member's medical record will be reviewed and any current authorizations for SMN modifying therapy will be terminated upon Zolgensma approval.

Exclusions

- The safety and effectiveness of repeat administration of Zolgensma has not been evaluated in clinical trials and therefore is considered investigational.
- The use of Zolgensma in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated in clinical trials and therefore is considered investigational.
- Use of Zolgensma in premature neonates before reaching full term gestational age is not recommended because concomitant treatment with corticosteroids may adversely effect neurological development. Delay Zolgensma infusion until full-term gestational age is reached.
- The use of Zolgensma in patients with one copy of SMN2 has not been evaluated in clinical trials and therefore is considered investigational. All subjects in the Phase 1 and Phase 3 pivot trial clinical trials had two copies of SMN2.
- Antepartum use of Zolgensma has not been evaluated in clinical trials and therefore is considered investigational.

Coding

The following codes are included below for informational purposes only; inclusion of a code does not constitute or imply coverage or reimbursement.

ICD-10 Diagnosis Codes

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

HCPCS Codes

Code	Description
J3399	Injection, onasemnogene abeparvovec-xioi, per treatment, up to 5x1015 vector genomes

MassHealth Acute Hospital Carve-Out Drugs List

Zolgensma is on the MassHealth Acute Hospital Carve-out Drugs List. In accordance with **MassHealth Managed Care Entity Bulletin 42**, Fallon Health requires hospitals to take the following actions with respect to drugs and biologics on the MassHealth Acute Hospital Carve-Out List for MassHealth ACO plan members:

1. Drugs and biologics on the MassHealth Acute Hospital Carve-Out Drugs List require prior authorization. The hospital must obtain prior authorization for the drug or biologic from Fallon Health. This prior authorization is separate from any prior authorization that may be required for the member's inpatient or outpatient encounter.
2. A drug or biologic designated by MassHealth as a carve-out drug must not be included on the facility/institutional claim that the hospital submits for the plan member's inpatient or outpatient encounter.
3. The hospital must instead submit a separate claim for the carve-out drug on a facility/institutional claim form (i.e., UB-04). (In other words, the drug is the only item on the UB-04 claim.) The charge reported on the claim must be the "hospital's actual acquisition cost" for the drug.*
4. The claim for the carve-out drug must be reported with revenue code 0636 (Drugs requiring detailed coding), the HCPCS code for the drug, the National Drug Code (NDC) for the drug, and number of units of the carve-out drug administered to the member.
5. The hospital must also include the following as separate attachments to the claim:
    a. A statement of the hospital's actual acquisition cost of the carve-out drug (as defined below) used to treat the member; and
    b. A copy of the invoice(s) for the carve-out drug from the drug manufacturer, supplier, distributor, or other similar party or agent; and
    c. Other additional documentation that the Plan deems necessary to evidence the hospital's actual acquisition cost of the carve-out drug.

* For purposes of this requirement, the "hospital's actual acquisition cost" of the carve-out drug is defined as follows:
"…*the hospital's invoice price for the drug, net of all on-or-off invoice reductions, discounts, rebates, charge backs and similar adjustments that the hospital has or will receive from the drug manufacturer or other party for the drug that was administered to the member including any efficacy, outcome, or performance-based guarantees (or similar arrangements), whether received pre-or post-payment*."

The MassHealth Acute Hospital Carve-out Drugs List is available at: https://masshealthdruglist.ehs.state.ma.us/MHDL/. This list may be updated from time to time.

Claims for Zolgensma (J3399) for MassHealth ACO and NaviCare plan members must be submitted with the 11-digit NDC Code. When reporting an NDC, all of the following NDC information is required:

- NDC Qualifier (F4)
- NDC Unit of Measure Qualifier (F2, GR, ME, UN, ML)
- NDC quantity

References

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Policy history

Origination date:	09/01/2021
Approval(s):	Technology Assessment Committee: 06/22/2021 (policy origination)

Not all services mentioned in this policy are covered for all products or employer groups. Coverage is based upon the terms of a member's particular benefit plan which may contain its own specific provisions for coverage and exclusions regardless of medical necessity. Please consult the product's Evidence of Coverage for exclusions or other benefit limitations applicable to this service or supply. If there is any discrepancy between this policy and a member's benefit plan, the provisions of the benefit plan will govern. However, applicable state mandates take precedence with respect to fully-insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, federal mandates will apply to all plans.