Zolgensma™ (onasemnogene abeparvovec-xioi)

Descriptive Narrative

Spinal muscular atrophy (SMA) is the second most common fatal autosomal recessive disorder after cystic fibrosis with an estimated incidence of 1 in 6,000 to 1 in 10,000 live births. It is caused by the lack of the survival motor neuron protein due to autosomal recessive mutations in the primary survival motor neuron (SMN1) gene. The absence of this protein results in the slow degeneration of the lower motor neurons in the spinal cord and somatic motor nuclei in the brainstem. In people with this condition symmetric progressive muscle atrophy and weakness develop. The weakness eventually encompasses all skeletal muscles leading to the inability to eat safely or breathe unassisted and eventual premature death.

Despite the relative SMN1 genotypic homogeneity in affected individuals there is quite a phenotypic range with five known types based on clinical features. Type 0 refers to those with neonatal onset of symptoms who are so severely affected that they often die in utero or shortly after birth. Type 1 is the most common, representing approximately 50% of cases, and is characterized by disease onset prior to 6 months of age with the children never achieving the ability to sit unassisted. Type 2 refers to children who can sit but never able to walk. Type 3 refers to individuals who achieve the ability to walk but then lose that skill. Finally, type 4 refers to individuals who become symptomatic in adulthood. The phenotypic severity is generally related to the number of copies of the SMN2 gene present, in an inverse fashion.

In May 2019, the FDA approved onasemnogene abeparvovec-xioi (Zolgensma™) gene therapy for children less than 2 years old who have SMA caused by bi-allelic mutations in the SMN1 gene. A safe virus delivers a fully functional human SMN gene to the targeted motor neurons, which in turn improves muscle movement and function and also improves survival. A second treatment, Nusinersen (Spinraza™) was approved in 2016 and is currently covered by the Iowa Medicaid program for treatment of children and adults with SMA.

The clinical effectiveness of Zolgensma™ has been demonstrated by the comparison of results of completed and ongoing clinical trials to available natural history data of patients with infantile onset SMA. In clinical trials, participants had a genetically
confirmed diagnosis of SMA1, homozygous SMN1 exon 7 deletions, and one or two copies of SMN2. Patients with persistently elevated anti-AAV9 antibody titers (>1:50) have been excluded. Follow-up has been short in studies of Zolgensma™, and the durability of the effects is uncertain. If the expression of the gene therapy declines over time, the same treatment cannot be repeated because antibodies against the capsule of the vector capsid proteins are expected to form. Improvements in both the CHOP INTEND (Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders) scale and the Hammersmith Functional Motor Scale-Expanded score have been used to document effectiveness.

There have been no head-to-head clinical trials assessing Zolgensma™ and Spinraza™ for treatment of symptomatic SMA1, but an industry-supported indirect comparison using frequentist and Bayesian approaches concluded that the onasemnogene abeparvovec may have an efficacy advantage for survival, independence from permanent assisted ventilation, motor function, and motor milestones\(^1\). Spinraza requires drug administration every 4 months for life via lumbar puncture while Zolgensma is a single IV infusion. A cost-effectiveness analysis of using Zolgensma™ for SMA1 patients concluded that the Single-dose Zolgensma™ was cost-effective compared to chronic Spinraza™ for SMA1 patients.

Criteria

Zolgensma is proven and medically necessary for one treatment per lifetime for the treatment of SMA in patients who meet ALL of the following criteria:

Submission of medical records (e.g., chart notes, laboratory values) confirming the following:

1. The mutation or deletion of genes in chromosome 5q resulting in ONE of the following:
   - Homozygous gene deletion or mutation of SMN1 gene (e.g., homozygous deletion of exon 7 at locus 5q13); OR
   - Compound heterozygous mutation of SMN1 gene (e.g., deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 [allele 2]); AND one of the following:
2. Diagnosis of symptomatic SMA by a neurologist with expertise in the diagnosis of SMA; or BOTH of the following:
   - Diagnosis of likely Type I or II SMA based on the results of SMA newborn screening; AND
   - Submission of medical records (e.g., chart notes, laboratory values) confirming that patient has 3 copies or less of SMN2 gene AND
3. For use in a neonatal patient born prematurely, the full-term gestational age (38 weeks) has been reached AND one of the following:

\(^1\) Adv Ther. 2019 May;36(5):1164-1176
Patient is less than or equal to 6 months of age AND
Patient does not have advanced SMA at baseline (e.g., complete paralysis of limbs) or ALL of the following:
Patient is greater than 6 months of age, but less than 2 years of age; AND one of the following:
Patient has previously received Spinraza (nusinersen) for the treatment of Type I, or likely Type I or II SMA before 6 months of age with positive clinical response; AND
Submission of medical records (e.g., chart notes, laboratory values) confirming patient does not have advanced SMA as defined by the fact that the patient has not shown evidence of clinical decline while receiving Spinraza therapy; OR both of the following:
Patient has previously received Spinraza (nusinersen) for the treatment of later-onset SMA before 2 years of age with positive clinical response; AND
Submission of medical records (e.g., chart notes, laboratory values) confirming patient does not have advanced SMA as defined by complete paralysis of all limbs; OR

D. Patient has recently been diagnosed with symptomatic later-onset SMA within the previous 6 months; AND
Submission of medical records (e.g., chart notes, laboratory values) confirming patient does not have advanced SMA as defined by complete paralysis of all limbs; AND
Patient is less than or equal to 13.5 kg; AND
Dose to be administered does not exceed one kit of Zolgensma AND
Patient is not dependent on either of the following:
- Invasive ventilation or tracheostomy
- Use of non-invasive ventilation beyond use for naps and nighttime sleep, AND
Zolgensma is prescribed by a neurologist with expertise in the treatment of SMA; AND
Patient is not to receive routine concomitant SMN modifying therapy (e.g., Spinraza) (patient’s medical record will be reviewed and any current authorizations for SMN modifying therapy will be terminated upon Zolgensma approval; patient access to subsequent SMN modifying therapy will be assessed according to respective coverage policy of concomitant agent); AND
Physician attests that the patient will be assessed for the presence of anti-AAV9 antibodies and managed accordingly; AND
Physician attests that the patient will not receive Zolgensma if the most recent pretreatment anti-AAV9 antibody titer is above 1:50; AND
Physician attests that the patient, while under the care of the physician, will be assessed by one of the following exam scales during subsequent office visits for a period not to exceed 3 years
- Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scale during subsequent office visits while the patient is 2 to 3 years of age or younger; **OR**
- Hammersmith Functional Motor Scale Expanded (HFMSE) during subsequent office visits while the patient is 2 to 3 years of age or older **AND**
  - Physician acknowledges that Iowa Medicaid may request documentation, not more frequently than biannually, of follow-up patient assessment(s) including, but not necessarily limited to, serial CHOP INTEND or HFMSE assessments while the patient is under the care of the physician; **AND**
  - Patient will receive prophylactic prednisolone (or glucocorticoid equivalent) prior to and following receipt of Zolgensma within accordance of the United States Food and Drug Administration (FDA) approved Zolgensma labeling; **AND**
  - Patient will receive Zolgensma intravenously within accordance of the FDA approved labeling, 1.1 x 10^14 vector genomes (vg) per kg of body weight; **AND**
  - Patient has never received Zolgensma treatment in their lifetime; **AND**
  - Authorization will be for no longer than 60 days from approval or until 2 years of age, whichever is first.

**Zolgensma is NOT proven or medically necessary for:**
- The treatment of pre-symptomatic patients diagnosed by newborn screening who are unlikely to develop Type I or II SMA; **OR**
- The treatment of symptomatic later-onset SMA older than 2 years of age; **OR**
- SMA without chromosome 5q mutations or deletions; **OR**
- The routine combination treatment of SMA with concomitant SMN modifying therapy.

**References**

Zolgensma [package insert]. Bannockburn, IL; AveXis, Inc. May 2019


United Healthcare Commercial Medical Benefit Drug Policy: Zolgensma®
(onasemnogene abeparvovec-xioi)

Development of utilization management criteria may also involve research into other state Medicaid programs, other payer policies, consultation with experts and review by the Medicaid Clinical Advisory Committee (CAC). These sources may not be referenced individually unless they are specifically published and are otherwise applicable to the criteria at issue.

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