ZOLGENSMA® (ONASEMNOGENE ABEPARVOVEC-XIOI)

Policy Number: PHARMACY 316.1 T2 **Effective Date**: June 1, 2019

Instructions for Use

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Related Policy

- Review at Launch for New to Market Medications

CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General Benefits Package
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	No[1]
Precertification with Medical Director Review Required	No
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	All
Special Considerations	[1]Precertification is not required, however it is strongly recommended for this medication. While no penalty will be imposed for failure to request a pre-service review, if one is not requested, a medical necessity review will be conducted post-service to determine coverage. It is the referring physician's responsibility to provide medical documentation to demonstrate clinical necessity for the medication. As of **Oct. 1, 2019**, precertification **will** be required. Refer to the Clinical Policy titled Review at Launch for New to Market Medications.

COVERAGE RATIONALE

See Benefit Considerations

Zolgensma has been added to the Review at Launch program. Some members may not be eligible for coverage of this medication at this time. Refer the Clinical Policy titled Review at Launch for New to Market Medications for additional details.

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

- Submission of medical records (e.g., chart notes, laboratory values) confirming the following:
  - The mutation or deletion of genes in chromosome 5q resulting in **one** of the following:
    - Homozygous gene deletion or mutation (e.g., homozygous deletion of exon 7 at locus 5q13); **or**

        - Compound heterozygous mutation (e.g., deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 [allele 2])

    and
- **One** of the following:
    - Diagnosis of Type I SMA by, or in consultation with a neurologist with expertise in the diagnosis of SMA; **or**
    - **Both** of the following:
        - Diagnosis of likely Type I SMA based on the results of SMA newborn screening; **and**
        - Patient has 3 copies or less of SMN2

    and
- **One** of the following:
    - Patient is less than 6 months of age; **or**
    - **All** of the following:
        - Patient is greater than 6 months of age
        - Patient has previously received Spinraza (nusinersen) for the treatment of Type I, or likely Type I SMA as described in criteria above, with positive clinical response
        - Patient is less than 8 kg

    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, or in consultation with, 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-AAV antibodies and managed accordingly; **and**
- Patient will receive prophylactic prednisolone (or glucocorticoid equivalent) prior to and approximately 30 days following receipt of Zolgensma; **and**
- Patient will receive Zolgensma intravenously within accordance of the United States Food and Drug Administration approved labeling; **and**
- Patient has never received Zolgensma treatment in their lifetime.

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 SMA, for the treatment of Type II, Type III, Type IV SMA, or for SMA without chromosome 5q mutations or deletions.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Zolgensma (onasemnogene abeparvovec-xioi) is an adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.

Limitation 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

BACKGROUND

Spinal muscular atrophy (SMA) is a rare, autosomal recessive neuromuscular disease that affects the survival of motor neurons of the spinal cord.[2] SMA is caused by the deletion/mutation of the SMN1 gene.[2] The estimated annual incidence of SMA is 5.1 to 16.6 cases per 100,000 live births. Approximately 1/40 to 1/60 people are SMA carriers, equating to 3.5 to 5.2 million and 12 to 18 million individuals in the United States and Europe, respectively.[2-6] SMA is characterized by the degeneration of motor neurons of the spinal cord, resulting in hypotonia and muscle weakness. Five phenotypic subtypes of SMA (0-IV) have been described based on age of symptom onset and motor function achieved.[5] Current literature indicates that the number of copies of the SMN2 gene that a patient has is the best predictor of clinical phenotype. The table below summarizes the clinical and genetic characteristics of the SMA subtypes.[2-6]

Clinical SMA Diagnosis	% of SMA cases	Usual Number of SMN2 copies	Typical age of symptom onset	Life expectancy	Motor development
Type 0	Very rare	1	In utero	Death occurs shortly after birth	None
Type I	58%	2	< 6 months	< 24 months	Never able to sit
Type II	29%	2-4 (80% have 3 copies)	< 18 months	70% alive at 25 years	Unable to walk without assistance
Type III	13%	95% have ≥ 3 copies		May be normal	Able to stand and walk without assistance, but lose ability as disease progresses
Type IV	<5%	≥ 4	20-30 years	Normal	Ambulatory. May experience mild muscle weakness

Zolgensma (Onasemnogene abeparvovec, AVXS-101) is a one-time SMN1 gene replacement therapy that treats the root cause of SMA, deletion or loss of function of the SMN1 gene, by delivering a copy of the human SMN gene via an adeno-associated virus serotype 9 (AAV9), which crosses the blood-brain barrier. Zolgensma is designed with a self-complementary DNA structure and a continuous promoter that allows for immediate and sustained expression of SMN protein, providing a rapid onset of effect. Motor neurons are non-dividing cells; thus a stable SMN gene therapy supplemented would not expected to be lost as children grow, potentially allowing for long-term, sustained SMN protein expression with a one-time dose, and providing a durable therapeutic effect.[7-12]

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

HCPCS Code	Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

ICD-10 Diagnosis Code	Description
G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]
G12.1	Other inherited spinal muscular atrophy
G12.9	Spinal muscular atrophy, unspecified

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy titled: Acquired Rare Disease Drug Therapy Exception Process.

CLINICAL EVIDENCE

Type 1 SMA

A phase 1, open-label, single site, dose-escalation study (CL-101) evaluated the safety and efficacy of a one-time IV administration of Zolgensma in 15 patients with type 1 SMA with 2 copies of survival motor neuron 2 (SMN2) 9 months of age or younger who developed symptoms of SMA prior to 6 months of age. Three of the patients received a

low dose (6.7×10^{13} vg per kilogram of body weight), and 12 received a high dose (2.0×10^{14} vg per kilogram). The primary outcome was safety. The secondary outcome was the time until death or the need for permanent ventilatory assistance. As of the data cutoff for the manuscript publication on August 7, 2017, all 15 patients were alive and event-free at 20 months of age, as compared with a rate of survival of 8% in a historical cohort. In the high-dose cohort, a rapid increase from baseline in the score on the CHOP INTEND scale followed gene delivery, with an increase of 9.8 points at 1 month and 15.4 points at 3 months, as compared with a decline in this score in a historical cohort. Of the 12 patients who had received the high dose, 11 sat unassisted, 9 rolled over, 11 fed orally and could speak, and 2 walked independently. Elevated serum aminotransferase levels occurred in 4 patients and were attenuated by prednisolone.[11,12,14]

A follow up presentation of the CL-101 study showed that at all patients were alive and without the need for ventilation at 24 months. In the high dose cohort (cohort 2), all patients achieved at least one motor milestone with 11 of 12 achieving motor milestones rarely seen in the type 1 SMA population. All 11 patients who achieved these milestones were 6 months of age or less at the time of gene therapy administration. The one patient not experiencing advanced motor milestone achievement was 8 months of age at the time of gene therapy administration. Patients treated with Zolgensma had a marked, early, and rapid improvement in CHOP-INTEND score, in contrast with untreated SMA type 1 patients who experienced a 10.7-point drop in CHOP-INTEND scores from 6–12 months of age. At 24 months follow-up, patients had a mean CHOP-INTEND score increase of 25.4 points from baseline (n=12). Eleven of 12 patients achieved and maintained a score >40 points for a mean of 19.5 months. In contrast, one recent natural history study reported that SMA type 1 children neither achieve nor maintain CHOP-INTEND scores >40 points after 6 months of age. As of April 2018, the oldest subject in cohort 2 was 46.2 months of age with 40.6 months of follow-up.

A pivotal, Phase 3, multicenter, open-label trial (STRIVE) is currently underway evaluating the safety and efficacy of a one-time intravenous administration of Zolgensma in patients less than 6 months of age with type 1 SMA based on genetic confirmation of a bi-allelic mutation of the SMN1 gene with 1 or 2 copies of the SMN2 gene who are not dependent on invasive or non-invasive ventilatory support for greater than 6 hours a day. Enrollment in the study is complete with 22 patients with 2 copies of SMN2 receiving Zolgensma. The patient population and baseline characteristics closely match those studied in the CL-101 study. The mean baseline age was 3.7 months with a range of 0.5-5.9 months. The mean baseline CHOP-INTEND score was 32 (range 17-52). Early results of the first 6 patients enrolled in the STR1VE study suggest a rapid increase in CHOP-INTEND scores at 1 and 3 months post Zolgensma administration similar to what has be described in the CL-101 trial.[8,10]

Pre-Symptomatic Patients Likely to Develop Type 1 SMA

A phase 3, multicenter, open-label trial (SPR1NT) is currently underway evaluating the safety and efficacy of a one-time intravenous administration of Zolgensma in patients less than 6 weeks of age with SMA based on a genetic confirmation of a bi-allelic mutation of the SMN1 gene with 2 or 3 copies of the SMN2 who have yet to develop symptoms who have a baseline compound muscle action potential (CMAP) > 2 mV at baseline. Enrollment is underway with planned enrollment of at least 15 patients each in cohorts with 2 and 3 copies of SMN2 respectively. Patients are to receive a one-time intravenous administration of Zolgensma at a dose on 1.1×10^{14} vg per kg. As of August 2018, 3 patients have received Zolgensma in the trial with positive results reported in the one patient with data available.[9,15]

Prediction of SMA Phenotype Based on SMN2 Copy Number

As stated above, current literature indicates that the number of copies of the SMN2 gene that a patient has is the best predictor of clinical phenotype, however the correlation is not absolute. A recent publication assessed the correlation of SMN2 copy number to SMA phenotype in 3459 patients worldwide from reports published after 1999. Analysis of the North American cohort showed similar findings. Seventy-three percent of patients of patients with 2 copies were diagnosed with Type I SMA, accounting for 79% of all Type I SMA cases. Patients with 3 copies of SMN2 were the most numerous in the entire cohort accounting for approximately half of the cases. Fifteen percent of patients with 3 copies of SMN2 were diagnosed with Type I SMA. Approximately 15% of patients in the worldwide cohort had 4 copies of SMN2. Patients with 4 copies of SMN2 were highly unlikely to be diagnosed with Type I SMA as greater than 99% of cases were diagnosed with Type II or Type III SMA. Patients with 4 copies of SMN2 accounted for 0.2% of all cases diagnosed with type I SMA.[6, 19]

Type 2 SMA

A phase 1, multicenter, open-label, dose-escalation trial (STRONG) is currently underway evaluating the safety and efficacy of a one-time intrathecal administration of onasemnogene abeparvovec in patients with SMA based on a genetic confirmation of a bi-allelic mutation of the SMN1 gene with 3 copies of SMN2, who are able to sit but cannot stand or walk at the time of study entry. These patients would be classically considered patients with likely type 2 SMA. Patients will receive onasemnogene abeparvovec in a dose comparison safety study of two potential therapeutic doses (3 patients at each dose). Patients will be stratified in two groups, those < 24 months of age at time of dosing and those ≥ 24 months and < 60 months of age at time of dosing. Fifteen patients < 24 months will be enrolled and

twelve patients ≥ 24 < 60 months will be enrolled. The first cohort will enroll 3 patients (cohort 1) < 24 months of age who will receive intrathecal administration of 6.0 x 10^{13} vg of onasemnogene abeparvovec (Dose A). After review of the data from cohort 1 by the Data Safety Monitoring Board (DSMB), a determination will be made to advance to Dose B, in which 3 patients from cohort 2 will receive 1.2 x 10^{14} vg of onasemnogene abeparvovec intrathecally. This trial is currently ongoing with no data reported publically as of October 2018.[16]

Professional Societies

In the 2018 Cure SMA Working Group treatment algorithm, the working group stresses the need for early intervention through newborn screening to maximize the benefit of treatment. This treatment algorithm was published prior to the approval of onasemnogene abeparvovec. The group recommends the development of dependable and validated screening techniques to enable treatment of presymptomatic patients who may be more responsive to treatment than those already experiencing symptoms. For patients with SMA Types II or III with three or fewer copies of the *SMN2* gene, the group recommends immediate treatment with a disease modifying therapy and referral to both a neuromuscular specialist and a geneticist; for those with only one copy of *SMN2* who are symptomatic at birth, the group states that the attending physician should determine whether the patient and family would benefit from treatment. Lastly, patients with four copies of *SMN2* should be screened periodically for symptoms and referred to a geneticist to determine the exact number of *SMN2* copies, but the working group recommends against immediate treatment with a disease modifying therapy.[18]

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy, Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee. [*2019D0079A*]

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
06/01/2019	• New policy

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

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