ZOLGENSMA® (ONASEMNOGENE ABEPARVOVEC-XIOI)

Policy Number: CS2019D0079B **Effective Date**: June 25, 2019

Instructions for Use

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Commercial Policy
- Zolgensma® (Onasemnogene Abeparvovec-Xioi)

APPLICATION

This Medical Benefit Drug Policy does not apply to the state of Kansas.

COVERAGE RATIONALE

Zolgensma has been added to the Review at Launch program. Please reference the Medical Benefit Drug 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 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:
  - 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
- For use in a neonatal patient born prematurely, the full-term gestational age has been reached; **and**
- **One** of the following:
  - **Both** of the following:
    - Patient is less than or equal to 6 months of age
    - 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:
      - **Both** 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 the fact that the patient has not shown evidence of clinical decline while receiving Spinraza therapy;

or

- 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 the fact that patient's most recent CHOP INTEND score is greater than or equal to 40; **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 pre-treatment 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 UnitedHealthcare 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, 1.1×10^{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 14 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, for the treatment of symptomatic later-onset SMA older than 2 years of age, for SMA without chromosome 5q mutations or deletions, or for the routine combination treatment of SMA with concomitant SMN modifying therapy.

*UnitedHealthcare has established an internal registry where this is a potential outcome measure. This registry has been established to prioritize early access to an SMA therapy with promising early clinical evidence, yet with unique commercialization characteristics, while ensuring appropriate management as clinical data matures.

¥ For quality purposes only, this information will not be considered as part of the individual coverage decision.

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 federal, state or contractual requirements 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 and Coverage Determination Guidelines 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

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 $\geq$ 3 copies		May be normal	Able to stand and walk without assistance, but lose ability as disease progresses
Type IV	<5%	$\geq$ 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. The use of Zolgensma in premature neonates before reaching full term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development. Zolgensma infusion is to be delayed until full-term gestational age is reached. [1,7-12]

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 dosage received by patients in the low-dose cohort was one-third of the dosage received by patients in the high-dose cohort. However, the precise dosages of Zolgensma received by patients in this completed clinical trial are unclear due to a change in the method of measuring Zolgensma concentration, and to decreases in the concentration of stored Zolgensma over time. The retrospectively-estimated dosage range in the high-dose cohort is approximately 1.1×10^{14} to 1.4×10^{14} vg/kg. 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). The maintenance of scores of more than 40 points on the CHOP-INTEND scale has been considered to be clinically meaningful in SMA. 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. None of the patients in the low dose cohort were able to sit without support, or to stand or walk; in the high dose cohort, 9 of the 12 patients (75.0%) were able to sit without support for ≥ 30 seconds, and 2 patients (16.7%) were able to stand and walk without assistance. 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). As of March 2019, 19 of 20 patients (95%) who had reached 10.5 months of age survived without permanent ventilation and 13 of 15 patients (87%) who had reached 13.6 months of age were surviving without permanent ventilation. The average increase in CHOP-INTEND scores were 6.9, 11.7, and 14.3 at months 1, 3, and 5 respectively. Twenty-one of 22 (95%) patients achieved CHOP-INTEND score of 40 or greater. Eleven of 22 (50%) patients were able to sit without support at a mean age of 13.8 months. No patient screened for AAV9 antibodies had exclusionary AAV9 antibody titers. [8,10,22]

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 27 patients in cohorts with 2 and 3 copies of SMN2. Patients are to receive a one-time intravenous administration of Zolgensma at a dose on 1.1×10^{14} vg per kg. As of March 2019, 18 patients have received Zolgensma in the trial with positive interim results reported. [9,15,20]

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. Ninety-five percent of patients with type II SMA and 54% of patients with type III SMA had 3 copies or less of SMN2. 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 non-type I SMA, with approximately 90% of patients with 4 SMN2 copies developing type III SMA.. Patients with 4 copies or more of SMN2 accounted for 0.3% of all cases diagnosed with type I SMA and approximately 5% of all cases diagnosed with type II 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 with onset of SMA symptoms occurring before 12 months of age. 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 (cohort 1) will be enrolled and twelve patients ≥ 24 < 60 months (cohort 2) will be enrolled. The first cohort will enroll 3 patients (cohort 1) < 24 months of age who will receive intrathecal administration of 6.0×10^{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 less than 60 months of age will receive 1.2×10^{14} vg of onasemnogene abeparvovec intrathecally. After review of the data from cohort 1 by the Data Safety Monitoring Board (DSMB), a determination will be made to advance to Dose C, in which 3 patients from cohort 2 will receive 2.4×10^{14} vg of onasemnogene abeparvovec intrathecally. Three patients in cohort 1 received dose A. Based on demonstrated acceptable safety, three additional patients in cohort 2 received dose B. Given ongoing demonstration of acceptable safety, 13 additional patients in cohort 1 and 9 in cohort 2 were treated with dose B. Primary endpoints were safety/tolerability, optimal dose, ability to stand unsupported ≥3 sec (cohort 1), and Hammersmith Functional Motor Scale-Expanded score (cohort 2). As of March 2019 30 patients have been enrolled and received intrathecal onasemnogene abeparvovec. Interim data from this multicenter study showed improvements in motor function in patients with type 2 SMA. 44% of patients in cohort 1 gained motor milestones following treatment. 25% of patients in cohort 2 gained motor milestones following treatment. In patients greater than 24 months of age, the mean increase in HFMSE was 4.2 points after an average therapy duration of 7.5 months. In cohort 2, 50% of patients experienced a 3 point or greater increase in HFMSE after 1 month of treatment. No dose limiting toxicity was observed, permitting dose-escalation to dose C (2.4×10^{14} vg) in 2 patients aged less than 24 months. [16,21]

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 presymptomatic patients with SMA and 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]

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

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for Zolgensma (onasemnogene abeparvovec). Local Coverage Determinations (LCDs) do not exist at this time.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.
(Accessed January 11, 2019)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description

06/25/2019	**Template Update**
	• Reorganized policy template; relocated *Background* and *FDA* sections
	Coverage Rationale
	• Revised proven and medically necessary coverage criteria for the treatment of spinal muscular atrophy (SMA)
	• Revised list of **not proven or medically necessary** indications:
	  ○ Added:
	  ▪ Treatment of pre-symptomatic patients diagnosed by newborn screening who are unlikely to develop type II SMA
	  ▪ Routine combination treatment of SMA with concomitant SMN modifying therapy
	  ○ Replaced "treatment of *type II, type III, type IV* SMA" with "treatment of *symptomatic later-onset* SMA older than 2 years of age"
	• Added language to indicate:
	  ○ UnitedHealthcare has established an internal registry where [certain information identified by * in the policy] is a potential outcome measure; this registry has been established to prioritize early access to an SMA therapy with promising early clinical evidence, yet with unique commercialization characteristics, while ensuring appropriate management as clinical data matures
	  ○ [Certain] information [identified by † in the policy] is for quality purposes only and will not be considered as part of the individual coverage decision
	Supporting Information
	• Updated *Background*, *Clinical Evidence*, and *References* sections to reflect the most current information
	• Archived previous policy version CS2019D0079A

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.