Sample Letter of Medical Necessity

[Institution Letterhead]

[Today's Date]

[Name of Health Insurance Company]
[PO Box or Street Address]
[City], [State] [Zip Code]

Re: [Patient Name], [DOB], [Parent/Legal Guardian's Name]
Policy Number: [Policy Number]
Group Number: [Group Number]
Medicaid Number (if applicable): [Medicaid Number]
ICD-10 Code: [G12.0 Infantile SMA Type 1 (Werdnig-Hoffman); G12.1 Other inherited SMA; G12.8 Other SMAs and related syndromes; G12.9 SMA, unspecified]

EXPEDITED REVIEW REQUEST FOR TREATMENT WITH ZOLGENSMA® (onasemnogene abeparvovec-xioi)

Dear [Medical Director],

I am writing to request authorization for ZOLGENSMA gene therapy for my patient, [Patient name], [DOB], [patient weight], who has spinal muscular atrophy (SMA). [Patient name] was diagnosed on [diagnosis date], based on genetic test results [and clinical symptoms] [or through newborn screening]. The most recent evaluation was on [evaluation date]. Due to the rapid progression of motor neuron loss and the narrow window for therapeutic intervention, **I am requesting priority review and approval of ZOLGENSMA**.[1]

SMA is a rare, devastating genetic disease that causes progressive, irreversible motor neuron loss and consequent loss of neuromuscular innervation and muscle function.[1-5] Children affected with one of the most severe types of SMA (SMA Type 1 or infantile onset SMA) experience early and rapid onset of symptoms within the first 6 months of life.[1,3,4] The disease is characterized by severe muscle weakness, decline in respiratory, eating, and swallowing function and failure to achieve important motor milestones, such as sitting without support, speaking, crawling, and walking.[3,5] The rapid progressive nature of the disease may result in respiratory failure and the need for permanent ventilatory support.[6] If untreated, there is only an 8% event-free survival rate at the age of 20 months.[5] Evidence suggests that motor neuron loss in SMA Type 1 begins early in the perinatal period, indicating that early treatment is essential in modulating the rapid degeneration. Therefore, it is critical to intervene with available therapies at the earliest possible time following diagnosis to achieve maximal benefit and, if possible, treat prior to symptom development.[1]

ZOLGENSMA Clinical Trials Overview

ZOLGENSMA is an adeno-associated virus (AAV) 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.[7] ZOLGENSMA was not evaluated in patients with advanced SMA (eg, complete paralysis of limbs, permanent ventilator dependence). ZOLGENSMA is for single-dose intravenous infusion. The efficacy of ZOLGENSMA in pediatric patients <2 years of age with SMA was evaluated by 2 clinical trials in which patients experienced onset of clinical symptoms before 6 months of age. In a completed, open-label, single-arm Phase 3 clinical trial (N=22), ZOLGENSMA was evaluated in pediatric patients with infantile-onset SMA.[8] Efficacy was established on the basis of survival (defined as time from birth to either death or permanent ventilation) and achievement of developmental motor milestones, such as sitting without support.[7] Efficacy was also supported by assessments of ventilator use, nutritional support, and scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). The CHOP INTEND is an assessment of motor skills in patients with infantile-onset SMA.

Please see Indication and Important Safety Information, and accompanying Full Prescribing Information including Boxed Warning for Acute Serious Liver Injury and Acute Liver Failure.

Of the 22 enrolled patients, 20 (91%) patients achieved the co-primary endpoint of event-free survival at 14 months of age and at 18 months of age.[8] In addition to survival, assessment of the other co-primary efficacy endpoint found that 59% (13/22) achieved the ability to sit without support for 30 seconds at the 18 month of age visit. A secondary outcome, ability to thrive, was defined as achieving all of the following at 18 months of age:

- Does not receive nutrition through mechanical support or other non-oral method
- Ability to tolerate thin liquids as demonstrated through a formal swallowing test
- Maintains weight

9/22 (40.9%) patients were able to meet all 3 components of the stringent composite measure of ability to thrive criteria at 18 months of age.[8]

In a separate Phase 1 clinical study (completed), 15 patients with infantile-onset SMA were enrolled in an open-label, single-arm, dose-escalating clinical trial, with 3 patients in a low-dose cohort and 12 in a high-dose cohort.[7] By 24 months following ZOLGENSMA infusion, 1 patient in the low-dose cohort met the endpoint of permanent ventilation. All 12 patients in the high-dose cohort were alive without permanent ventilation. In the high-dose cohort, 75% (9/12) were able to sit without support for ≥30 seconds and 16.7% (2/12) were able to stand and walk without assistance.

I am recommending therapy for [Patient Name], based on [his/her] diagnosis and genetic test results, [current symptoms], and the opportunity to stop the progression of the disease and preserve critical motor functions. The sooner I can treat [Patient Name], the higher the likelihood of a better outcome.[4] Delaying treatment may result in further motor neuron loss.[6] Individuals with SMA may lose significant motor function in the first 8-12 weeks of age.[1,9] Clinical data suggest that there is a benefit to early treatment as demonstrated by milestones achieved in patients who are treated early.[1,4,6]

[Symptomatic Patient Summary]:

[Patient Name] was diagnosed at age [x months of age] and has current symptoms of [list of current symptoms]. [Patient Name]'s [CHOP INTEND or other motor function score] is [xx]. Without treatment, [Patient Name] may be expected to experience a rapid and progressive decline in function.[1] With therapy, the goal is to maintain and/or improve motor function and stop the progression of the disease. Without treatment, [state patient's prognosis and associated costs].

[Please insert your own medical rationale for ZOLGENSMA].

[Presymptomatic Patient Summary]:

[Patient Name] was diagnosed at age [age at diagnosis], [through newborn screening, if applicable]. Due to the early diagnosis, [Patient Name] has the best possible prognosis if treated before the onset of significant motor loss and associated symptoms.[1] Based on the genetic test results and natural history, patients with SMA Type 1 are expected to lose the ability to breathe, swallow, and move independently, and will never sit unassisted, crawl, or walk.[3-5] Patients with SMA Type 2 are expected to be unable to walk without support and patients with SMA Type 3 may achieve the ability to stand and walk without support until the disease progresses.[10]

[Please insert your own medical rationale for ZOLGENSMA].

Assessment:

Based on the natural history progression of SMA Type 1, rapid, permanent loss of motor function is expected without treatment.[5,11] If untreated, [Patient Name] will likely experience severe medical consequences and require mechanical ventilation and nutritional support by the age of 12 months, with a high risk of permanent ventilation or death prior to the age of 2 years.[4,5,11] Early treatment with disease-modifying therapy may halt the progression of the disease and prevent further motor neuron loss.[1] Early treatment has also been shown to reduce associated medical complications, including ventilatory support, nutritional support, permanent ventilation, and death.[1,6]

[Please insert your own medical rationale for ZOLGENSMA].

Recommended Intervention:

Recommended Intervention of Individuals with 2 or 3 Copies of *SMN2*:
In a Phase 3 clinical study, SPR1NT, early initiation of treatment prior to the development of symptoms in infants diagnosed with SMA, and with 2 or 3 copies of *SMN2*, demonstrated substantial clinical benefit.[12-14]

- Of the 29 enrolled patients, all 29 (100%) patients were alive and achieved the primary endpoints:
  - Patients with 2 copies of *SMN2* achieved functional independent sitting,* according to the Bayley definition, up to the 18 months of age visit
    - 11 of 14 achieved this milestone within an age-appropriate time period
  - Patients with 3 copies of *SMN2* achieved standing alone,† according to the Bayley definition, up to the 24 months of age visit
    - 14 of 15 achieved this milestone within an age-appropriate time period
- 23/29 patients achieved the exploratory and secondary endpoint of walking alone
  - ~64%; 9/14 patients with two *SMN2* copies achieved the exploratory endpoint of walking alone,‡ according to the Bayley definition, up to the 18 months of age visit
    - 5 of 14 achieved this milestone within an age-appropriate time period
  - ~93%; 14/15 patients with three *SMN2* copies achieved the secondary endpoint of walking alone,‡ according to the Bayley definition, up to the 24 months of age visit
    - 11 of 15 achieved this milestone within an age-appropriate time period
- Patients also achieved exploratory endpoints of standing alone and standing with assistance
  - ~79%; 11/14 patients with two *SMN2* copies achieved standing alone,† according to the Bayley definition, up to the 18 months of age visit
    - 7 of 14 achieved this milestone within an age-appropriate time period
  - ~93%; 14/15 patients with three *SMN2* copies achieved standing with assistance,§ according to the WHO-MGRS definition, up to the 24 months of age visit
    - 11 of 15 achieved this milestone within an age-appropriate time period

With early treatment, ZOLGENSMA enabled patients to achieve age-appropriate gross motor development. Approximately 64% (9/14) of patients with 2 copies of *SMN2*, and 100% (15/15) of patients with 3 copies of *SMN2*, treated with ZOLGENSMA had gross motor performance similar to same-aged peers.[13,14]

Recommended Intervention of Individuals with 4 Copies of *SMN2*:
In 2019, a group of expert clinicians and scientists convened by Cure SMA recommended immediate treatment for infants diagnosed with SMA via newborn screening (NBS) with 4 copies of *SMN2*. The number of *SMN2* copies may predict the severity of SMA. Approximately 96% of patients with SMA Type 3 carry 3 or 4 copies of *SMN2*. In patients with 4 copies of *SMN2*, the probabilities of developing SMA Types 2 and 3 were 14.8% and 83.6%, respectively.[16] Previous studies have shown that presymptomatic treatment may have a positive effect on those with 3 copies of *SMN2*.[14] Further, the working group states that with early treatment, similar outcomes could be predicted in patients with 4 copies of *SMN2*.[15]

In summary, I am requesting an expedited review and approval to treat my patient with SMA, [Patient Name], with ZOLGENSMA. In my professional opinion, ZOLGENSMA is medically necessary for the treatment of this patient and offers [him/her] a significantly improved prognosis over the natural course of the disease [specify again the specific motor milestones you expect this patient to achieve (eg, avoidance of ventilation, ability to sit, feed, stand, crawl, walk) based on clinical trial results].[4-6] ZOLGENSMA may deliver substantial survival benefit with an expected lifetime cost that is less than or similar to the cost of lifelong, ongoing treatments.[17] I have reviewed the possible benefits of this treatment and mode of delivery with the patient's parents/legal guardians, and counseled them on the risks associated with this treatment.
[Please insert your own medical rationale or relevant documentation, such as chart notes or lab results, for ZOLGENSMA].

Sincerely,
[Prescriber Name, Credentials, Title, Signature]

Age-appropriate time periods were defined according to the WHO-MGRS established windows of achievement for the development of motor milestones.
WHO-MGRS=World Health Organization Multicentre Growth Reference Study.
*Bayley Scales Gross Motor Subtest Item #26: Sits without support for at least 30 seconds.[13]
†Bayley Scales Gross Motor Subtest Item #40: Stands alone for at least 3 seconds.[14]
‡Bayley Scales Gross Motor Subtest Item #43: Walks alone.[13,14]
§WHO-MGRS definition: Stands with assistance for at least 10 seconds.[14]

Indication and Important Safety Information for ZOLGENSMA® (onasemnogene abeparvovec-xioi)

Indication
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.
Limitations of Use
The safety and effectiveness of repeat administration or the use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated with ZOLGENSMA.

Important Safety Information
BOXED WARNING: Acute Serious Liver Injury and Acute Liver Failure
Acute serious liver injury, acute liver failure, and elevated aminotransferases can occur with ZOLGENSMA. Patients with preexisting liver impairment may be at higher risk. Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Administer a systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion.

WARNINGS AND PRECAUTIONS
Thrombocytopenia
Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were typically observed within the first two weeks after ZOLGENSMA infusion. Monitor platelet counts before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards.

Thrombotic Microangiopathy
Cases of thrombotic microangiopathy (TMA) were reported approximately 1 week after ZOLGENSMA infusion. Obtain baseline creatinine and complete blood count before ZOLGENSMA infusion. Following infusion, monitor for thrombocytopenia as well as other signs and symptoms of TMA. Consult a pediatric hematologist and/or pediatric nephrologist immediately to manage if clinically indicated.

Please see Indication and Important Safety Information, and accompanying Full Prescribing Information including Boxed Warning for Acute Serious Liver Injury and Acute Liver Failure.

Elevated Troponin-I
Increases in cardiac troponin-I levels were observed following ZOLGENSMA infusion. Monitor troponin-I before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards.

ADVERSE REACTIONS
The most commonly observed adverse reactions (incidence ≥5%) in clinical studies were elevated aminotransferases and vomiting.

Please see Full Prescribing Information.

References: 1. Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. *J Neuromuscul Dis.* 2018;5(2):145-158. **2.** Hamilton G, Gillingwater TH. Spinal muscular atrophy: going beyond the motor neuron. *Trends Mol Med.* 2013;19(1):40-50. **3.** Anderton RS, Mastaglia FL. Advances and challenges in developing a therapy for spinal muscular atrophy. *Expert Rev Neurother.* 2015;15(8):895-908. **4.** Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med.* 2017;377(18):1713-1722. **5.** Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology.* 2014;83(9):810-817. **6.** Lowes LP, Alfano LN, Arnold WD, et al. Impact of age and motor function in a phase 1/2A study of infants with SMA type 1 receiving single-dose gene replacement therapy. *Ped Neurol*. 2019;98:39-45. **7.** ZOLGENSMA [prescribing information]. Bannockburn, IL: Novartis Gene Therapies, Inc; 2021. **8.** Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of *SMN2* (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. *Lancet Neurol*. 2021;20(4):284-293. **9.** Swoboda KJ. SMN-targeted therapeutics for spinal muscular atrophy: are we SMArt enough yet? *J Clin Invest.* 2014;124(2):487-490. **10.** Trundell D, Le Scouiller S, Le Goff L, et al. Assessment of the validity and reliability of the 32-item Motor Function Measure in individuals with Type 2 or non-ambulant Type 3 spinal muscular atrophy. *PLoS ONE*. 2020;15(9):e0238786. **11.** Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol.* 2017;82(6):883-891. **12.** Novartis Gene Therapies, Inc. Pre-symptomatic study of intravenous onasemnogene abeparvovec-xioi in spinal muscular atrophy (SMA) for patients with multiple copies of *SMN2* (SPR1NT). https://clinicaltrials.gov/ct2/show/NCT03505099. ClinicalTrials.gov identifier: NCT03505099. Updated January 11, 2022. Accessed March 4, 2022. **13.** Data on file. Novartis Gene Therapies, Inc. 2021. **14.** Data on file. Novartis Gene Therapies, Inc. 2022. **15.** Glascock J, Sampson J, Connolly AM, et al. Revised recommendations for the treatment of infants diagnosed with spinal muscular atrophy via newborn screening who have 4 copies of *SMN2*. *J Neuromuscul Dis.* 2020;7(2):97-100.**16.** Feldkötter M, Schwarzer V, Wirth R, et al. Quantitative analyses of *SMN1* and *SMN2* based on real-time LightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. *Am J Hum Genet*. 2002;70(2):358-368. **17.** Malone DC, Dean R, Arjunji R, et al. Cost-effectiveness analysis of using onasemnogene abeparvovec (AVXS-101) in spinal muscular atrophy type 1 patients. *J Mark Access Health Policy*. 2019;7(1):1601484**.**

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Bannockburn, IL 60015

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