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-CM 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) suspension for intravenous infusion

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] [and 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 six months of life.[1,3,4] The disease is characterized by severe muscle weakness, decline in respiratory, eating, and swallowing functions 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. Outcomes with presymptomatic SMA treatment are improved when more motor neurons are still viable.[7,8] An expert panel assembled by Cure SMA recommends immediate, presymptomatic treatment of SMA in infants identified by newborn screening (NBS) with up to four copies of *SMN2* to achieve maximal therapeutic benefit.[1,9] 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 two years of age with SMA with bi-allelic mutations in the *survival motor neuron 1* (*SMN1*) gene.[10] 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 less than two years of age with SMA was evaluated by two clinical trials in which patients experienced onset of clinical symptoms before six months of age. In the STR1VE-US open-label, single-arm, phase III clinical trial (N=22), ZOLGENSMA was evaluated in pediatric patients with infantile-onset SMA.[11] 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.[10] 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).[10] The CHOP INTEND is an assessment of motor skills in patients with infantile-onset SMA.

Of the 22 enrolled patients, 20 (91%) patients achieved the coprimary endpoint of event-free survival at 14 months of age and at 18 months of age.[11] In addition to survival, assessment of the other coprimary efficacy endpoint found that 59% (13 out of 22) of patients achieved the ability to sit without support for 30 seconds at the 18-months-of-age visit.[11] A secondary outcome, ability to thrive, was defined as achieving all of the following at 18 months of age[11]:

- Does not receive nutrition through mechanical support or other nonoral method
- Is able to tolerate thin liquids as demonstrated through a formal swallowing test
- Maintains weight

Nine out of 22 (40.9%) patients were able to meet all three components of the stringent composite measure of ability to thrive criteria at 18 months of age.[11]

In the START phase I clinical study, 15 patients with infantile-onset SMA were enrolled in an open-label, single-arm, dose-escalating clinical trial, with three patients in a low-dose cohort and 12 in a high-dose cohort.[10] By 24 months following ZOLGENSMA infusion, one patient in the low-dose cohort met the endpoint of survival without permanent ventilation. All 12 patients in the high-dose cohort were alive without permanent ventilation. In the high-dose cohort, 75% (nine out of 12) of patients were able to sit without support for ≥30 seconds and 16.7% (two out of 12) of patients were able to stand and walk without assistance.[10]

Thirteen patients who completed the START study enrolled in LT-001, an ongoing, 15-year, long-term follow-up study; three in the low-dose cohort and 10 in the high-dose (therapeutic dose) cohort. As of May 23, 2022, all 13 patients were followed for a mean of 95.1 (low-dose) and 83.5 (high-dose) months.[12]

- No deaths or serious adverse events (SAEs) related to treatment were reported
- All 10 patients who received the therapeutic dose survived and were free of permanent ventilation (mean [range] age at last data cut, 7.1 [6.6-7.9] years)
- LT-001 demonstrated durable efficacy with a single therapeutic dose up to 7.5 years post-dosing

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 eight to 12 weeks of life.[1,13] 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.[14]

[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.[5,15] 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 two years.[4,5,15] 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 Two or Three Copies of the *Survival Motor Neuron 2* (*SMN2*) Gene:
In a phase III clinical study, SPR1NT, early initiation of treatment prior to the development of symptoms in infants diagnosed with SMA, and with two or three copies of *SMN2*, demonstrated substantial clinical benefit.[16-18]

- Of the 29 enrolled patients, all 29 (100%) patients were alive and achieved the primary endpoints:
  - Patients with two copies of *SMN2* achieved functional independent sitting,* according to the Bayley definition, up to the 18-months-of-age visit
    - Eleven out of 14 patients achieved this milestone within an age-appropriate time period
  - Patients with three copies of *SMN2* achieved standing alone,† according to the Bayley definition, up to the 24-months-of-age visit
    - Fourteen out of 15 patients achieved this milestone within an age-appropriate time period
- Twenty-three out of 29 patients achieved the exploratory and secondary endpoint of walking alone
  - Approximately 64% (nine out of 14) of patients with two copies of *SMN2* achieved the exploratory endpoint of walking alone,‡ according to the Bayley definition, up to the 18-months-of-age visit
    - Five patients achieved this milestone within an age-appropriate time period
  - Approximately 93% (14 out of 15) of patients with three copies of *SMN2* achieved the secondary endpoint of walking alone,‡ according to the Bayley definition, up to the 24-months-of-age visit
    - Eleven patients achieved this milestone within an age-appropriate time period
- Patients also achieved exploratory endpoints of standing alone
  - Approximately 79% (11 out of 14) of patients with two copies of *SMN2* achieved standing alone,† according to the Bayley definition, up to the 18-months-of-age visit
    - Seven patients achieved this milestone within an age-appropriate time period

With early treatment, ZOLGENSMA enabled patients to achieve age-appropriate gross motor development. Approximately 64% (nine out of 14) of patients with two copies of *SMN2*, and 100% (15 out of 15) of patients with three copies of *SMN2*, treated with ZOLGENSMA had gross motor performance similar to normally developing same-aged peers.[17,18]

Demonstrated Durability of Treatment in Ongoing, Long-Term, Follow-Up Study (LT-002)

LT-002 enrolled 67 patients who completed the STR1VE and SPR1NT studies; 41 patients from STR1VE-US, STR1VE-EU, and STR1VE-AP (symptomatic SMA type 1), and 26 from SPR1NT (presymptomatic). Among presymptomatic patients, 13 had two copies of *SMN2* and 13 had three copies of *SMN2*.[19]

As of the June 2024 data cut, the mean follow-up time since treatment was[19]

- 5.8 years for STR1VE-US (n=14)
- 5.4 years for STR1VE-EU (n=25)
- 3.9 years for STR1VE-AP (n=2)
- 5.0 years for SPR1NT patients with two copies of *SMN2* (n=13)
- 5.5 years for SPR1NT patients with three copies of *SMN2* (n=13)

Of the 68 patients, 27 (39.7%) had at least one adverse event, and 24 (35.3%) had at least one serious adverse event[19]

- The most frequently reported serious adverse event in >5% of patients was pneumonia, reported in 9 (13.2%) patients

Of the presymptomatic patients in LT-002[19]

- 100% (26 out of 26) of patients enrolled from the SPR1NT study achieved walking independently based on Bayley or WHO
- 100% (26 out of 26) remained free from ventilatory support of any kind, including invasive (eg, tracheostomy) or noninvasive (eg, BiPAP)
- 100% (13 out of 13) of patients with three copies of *SMN2* were free of feeding support, and 92.3% (12 out of 13) of patients with two copies of *SMN2* were free of feeding support at the data cut
- Most of the presymptomatically treated patients (25 out of 26) did not require nutritional support and none required ventilatory support for a mean of ~5 years in the long-term follow-up

Recommended Intervention of Individuals With Four 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 NBS with four copies of *SMN2*.[9] Patients with four copies of *SMN2* may develop signs of SMA despite there being an inverse correlation between disease severity and *SMN2* copy number. In patients with four copies of *SMN2*, the probabilities of developing SMA types 2 and 3 were 14.8% and 83.6%, respectively.[20]

The RESTORE Registry is an ongoing, prospective, multicenter, multinational, observational study to analyze treatment patterns and long-term outcomes in SMA. As of December 2022, an analysis of 19 patients with four or more copies of *SMN2* who received ZOLGENSMA monotherapy found that[21,22]

- Eleven out of 12 patients (six out of 11 had four copies of *SMN2*, five out of 11 had more than four copies) with recorded milestones, achieved them after treatment with ZOLGENSMA, including five patients who achieved walking alone and two who achieved standing alone
    - Three patients achieved milestones before and after treatment, and one patient achieved a new milestone only before treatment
- Four out of four patients with at least two assessments of CHOP INTEND achieved or maintained the maximum score of 64
    - Two patients had four copies of *SMN2* and two had more than four copies
- Two out of 3 patients with at least 2 assessments of HFMSE after ZOLGENSMA administration achieved a clinically meaningful ≥3 point improvement
    - All three patients had four copies of *SMN2*
- One patient with at least two assessments of HINE-2 after ZOLGENSMA administration achieved a 6-point increase
- Five out of 19 children had one or more TEAEs
    - One patient with more than four copies of *SMN2* reported a grade 4 TEAE, a seizure that resolved and from which they recovered
- No deaths or use of ventilatory or nutritional support were reported

- Transaminase elevations over three times the normal values were reported for 21% (four out of 19) patients
- No cases of acute liver failure or acute serious liver injury were reported
- All patients were asymptomatic at diagnosis

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.[23] 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.[17,18]
*Bayley Scales Gross Motor Subtest Item #26: Sits without support for at least 30 seconds.[17]
†Bayley Scales Gross Motor Subtest Item #40: Stands alone for at least 3 seconds.[18]
‡Bayley Scales Gross Motor Subtest Item #43: Walks alone.[17,18]
§One symptomatic patient reached permanent ventilation status during the study, defined as invasive ventilation or ≥16 hours/day of noninvasive ventilation support for ≥14 days in the absence of an acute reversible illness or perioperative care.
HINE-2, Hammersmith Infant Neurologic Examination Section 2; HFMSE, Hammersmith Functional Motor Scale—Expanded; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; TEAE, treatment-emergent adverse events; WHO-MGRS, World Health Organization Multicentre Growth Reference Study.

Indication and Important Safety Information for ZOLGENSMA® (onasemnogene abeparvovec-xioi)
INDICATION
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 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 (eg, complete paralysis of limbs, permanent ventilator dependence) has not been evaluated with ZOLGENSMA.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: Serious Liver Injury and Acute Liver Failure
Cases of acute liver failure with fatal outcomes have been reported. Acute serious liver injury, acute liver failure, and elevated aminotransferases can also 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. Administer systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion, and at other times as clinically indicated. If acute serious liver injury or acute liver failure is suspected, promptly consult a pediatric gastroenterologist or hepatologist.

WARNINGS AND PRECAUTIONS

Systemic Immune Response
Patients with underlying active infection, either acute or chronic uncontrolled, could be at an increased risk of serious systemic immune response. Administer ZOLGENSMA to patients who are clinically stable in their overall health status (eg, hydration and nutritional status, absence of infection). Postpone ZOLGENSMA in patients with infections until the infection has resolved and the patient is clinically stable.

Thrombocytopenia
Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were typically observed within the first 2 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 to occur generally within the first 2 weeks after ZOLGENSMA infusion. TMA can result in life-threatening or fatal outcomes. Obtain baseline creatinine and complete blood count before ZOLGENSMA infusion. Following infusion, monitor platelet counts closely as well as other signs and symptoms of TMA. Consult a pediatric hematologist and/or pediatric nephrologist immediately to manage as clinically indicated.

Elevated Troponin I
Increases in cardiac troponin I levels have occurred following ZOLGENSMA infusion. Consider cardiac evaluation after ZOLGENSMA infusion and consult a cardiologist as needed.

AAV Vector Integration and Risk of Tumorigenicity
There is a theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome. Cases of tumor have been reported in patients who received ZOLGENSMA post-approval; a causal relationship has not been established based on tumor analysis. In some cases, limited information was available. Report cases of tumor development in patients who received ZOLGENSMA to Novartis Gene Therapies, Inc. at 1-833-828-3947.

Infusion-Related Reactions
Infusion-related reactions, including hypersensitivity reactions and anaphylaxis, have occurred with ZOLGENSMA infusion. Signs and symptoms may include rash, urticaria, vomiting, dyspnea, respiratory symptoms, and/or alterations in heart rate and blood pressure. Monitor patients during and after treatment with ZOLGENSMA. If an infusion-related reaction occurs, interrupt ZOLGENSMA infusion and administer supportive treatment to manage the infusion-related reaction as appropriate. Infusion of ZOLGENSMA may be resumed based on clinical assessment.

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.** Jędrzejowska M. Advances in newborn screening and presymptomatic diagnosis of spinal muscular atrophy. *Degener Neurol Neuromuscul Dis*. 2020;10:39-47. **8.** Dangouloff T, Servais L. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: current perspectives. *Ther Clin Risk Manag*. 2019;15:1153-1161. **9.** 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. **10.** ZOLGENSMA. Prescribing information. Novartis Gene Therapies, Inc. **11.** 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. **12.** Data on file. Novartis Gene Therapies, Inc. 2023. **13.** Swoboda KJ. *SMN*-targeted therapeutics for spinal muscular atrophy: are we SMArt enough yet? *J Clin Invest.* 2014;124(2):487-490. **14.** 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. **15.** Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol.* 2017;82(6):883-891. **16.** 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). ClinicalTrials.gov identifier: NCT03505099. Updated September 7, 2022. Accessed February 12, 2025. https://clinicaltrials.gov/ct2/show/NCT03505099 **17.** Strauss KA, Farrar MA, Muntoni P, et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of *SMN2* at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial. *Nat Med*. 2022;28(7):1381-1389. doi:10.1038/s41591-022-01866-4 **18.** Strauss KA, Farrar MA, Muntoni P, et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of *SMN2* at risk for spinal muscular atrophy: the Phase III SPR1NT trial. *Nat Med*. 2022;28(7)1390-1397. doi:10.1038/s41591-022-01867-3 **19.** Data on file. Novartis Pharmaceuticals Corp; 2025. **20.** 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. **21.** Tizzano EF, Quijano-Roy S, Servais L, RESTORE Study Group, et al. Outcomes for patients in the RESTORE registry with spinal muscular atrophy and four or more *SMN2* gene copies treated with onasemnogene abeparvovec. *Eur J Pediatr Neurol*. 2024;53:18-24. **22**. Tizzano EF, Quijano-Roy S, Servais L, RESTORE Study Group, et al. Outcomes for patients in the RESTORE registry with spinal muscular atrophy and four or more *SMN2* gene copies treated with onasemnogene abeparvovec. *Eur J Pediatr Neurol*. Supplementary data. Published online August 26, 2024. doi:10.1016/j.ejpn.2024.08.006 **23.** 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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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080 2/25 FA-11357445