Illinois Department of Healthcare and Family Services (HFS)
University of Illinois at Chicago – College of Pharmacy

Prior Authorization Internal Criteria – **DRAFT 8.15.19 -Final**
Zolgensma

Rationale

Zolgensma is a gene replacement therapy for the treatment of spinal muscular atrophy (SMA).[1] SMAs are neuromuscular disorders that result in progressive muscle atrophy and weakness.[2] The most common form is caused by a deletion or mutation in the survival motor neuron 1 (*SMN1*) gene. The most severe form is SMA Type I, which is characterized by an age of onset of ≤6 months. SMA Type II manifests symptoms after 6 months of age up to 18 months. SMA Type III has an age of onset greater than 18 months, while SMA Type IV occurs in the second to third decades of life. The *SMN2* gene serves as a backup for the *SMN1* gene to produce low levels of the SMN protein.[3] Patients with more copies of the *SMN2* gene generally have a less severe form of SMA. Most patients with SMA Type I carry 2 *SMN2* copies, while patients with Type II usually have 3 copies of *SMN2*, and patients with Type III may have 3-4 copies of the *SMN2* gene.

Zolgensma induces SMN gene expression by delivering a copy of the human *SMN* gene to the cell nucleus through the adeno-associated virus serotype 9 (AAV9) capsid.[1] It is administered as a one-time dose by intravenous (IV) infusion. It is dosed at 1.1×10^{14} vg/kg of weight.[4] Prior to the infusion, testing for liver function, platelets, troponin-I, and anti-AAV9 antibodies must be performed. Starting on the day before the infusion, systemic corticosteroids equivalent to prednisolone 1 mg/kg/day must be administered for a total of 30 days. After 30 days, liver function tests including AST, ALT, total bilirubin, and prothrombin time should be repeated. If the liver function tests are unremarkable, the corticosteroids may be tapered off. However, if the liver function tests are abnormal, corticosteroids should be continued until all levels are < 2 x ULN and then corticosteroids should be tapered over 28 days.

START was a phase 1, open-label, dose-escalation study that evaluated the safety and efficacy of Zolgensma for patients with SMA Type 1.[1] The study consisted of 2 cohorts based on dosing: cohort 1 received a low dose of 6.7×10^{13} vg/kg, while cohort 2 received a high dose of 2.0×10^{14} vg/kg. The efficacy endpoint studied was time until death or the need for permanent ventilator assistance, defined as ≥16 hours of respiratory assistance continuously for at least 14 days. Other efficacy outcomes studied were motor milestones achieved and CHOP INTEND score. Safety outcomes included the occurrence of any adverse events (grade 3 or higher). The mean age at time of treatment for cohort 1 was 6.3 months and 3.4 months for cohort 2. As of August 7, 2017, no deaths were reported and all patients reached an age of ≥20 months, with no participants requiring permanent mechanical ventilation. At the end of the study, cohort 1 had a mean increase of 7.7 points and cohort 2 had a mean increase of 24.6 points in their CHOP INTEND scores. For cohort 2, 91.6% of patients were able to sit unassisted for ≥5 seconds, 91.6% were able to achieve head control, 91.6% were able to speak, and 75% were able to roll over. For safety outcomes, two patients had elevated liver enzymes, requiring prednisolone treatment.

Of the 12 patients in Cohort 2, 10 enrolled in a long-term follow-up study.[5] As of March 8, 2019, no deaths or need for permanent ventilation were reported. The average time since treatment was 3.7 years and the mean age was 3.9 years. All motor function milestones were maintained from the START trial. In the long-term study, 70% of patients remained on monotherapy with Zolgensma. Initiation of combination therapy, with Spinraza was at parental and physician discretion.

STR1VE is an ongoing, open-label, phase 3 study evaluating the safety and efficacy of Zolgensma for the treatment of SMA Type I.[6,7] Patients were confirmed to have *SMN1* gene deletion or point mutations with up to 2 copies of the *SMN2* gene. Patients were ≤6 months of age at the time of drug administration. Interim data as of March 8, 2019 demonstrated a 95% survival rate without permanent ventilation. One patient died from respiratory failure, which was considered unrelated to treatment. The CHOP-INTEND scores increased by 6.9 points one month after treatment, 11.7 points 3 months after treatment, and 14.3 points 5 months after treatment. The interim data demonstrated an increase in milestones achieved, with 47.6% of patients sitting without support for ≥30 seconds. Adverse effects included elevated liver enzymes and thrombocytopenia.

SPR1NT is an open-label, phase 3 trial evaluating the safety and efficacy of Zolgensma in pre-symptomatic patients with SMA.[7] Patients with up to 3 copies of the *SMN2* gene were included in the trial. Patients were ≤6 weeks of age at the time of drug administration. Patients had a gestational age of 35 to 42 weeks. The primary outcome for those with 2 copies of *SMN2* gene is independent sitting for ≥30 seconds by 18 months. The primary outcome for those with 3 copies of *SMN2* gene is standing for ≥3 seconds by 24 months. As of March 8, 2019, all patients were alive and without permanent ventilation. For patients with 2 copies of *SMN2* gene, the mean increase in CHOP-INTEND score was 8.9 points one month after treatment. At a median age of 6.1 months, 22% percent of patients were able to achieve the primary outcome.

There are several ongoing trials including:

- STRONG, a phase 1, open label, dose comparison trial to evaluate the safety and efficacy of a one-time intrathecal administration of Zolgensma in patients with SMA Type 2. Patient with up to 3 copies of the *SMN2* gene were included in the trial. Patients were stratified by age at time of dosing: patients ≥6 months but <24 months, and patients ≥24 months but <60 months. For those patients <24 months of age at time of dosing, the primary end point is the ability to stand without support. For those ≥24 months at time of dosing, the primary endpoint is change in Hammersmith Functional Motor Scale – Expanded (HFMSE) score from baseline.
- STR1VE-EU, a phase III, single dose, open label study evaluating the safety and efficacy of a one-time IV infusion of Zolgensma in patients with SMA Type I.
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Approval Criteria

1. Participant has diagnosis of spinal muscular atrophy (SMA), confirmed with documentation of bi-allelic mutations in the *SMN1* gene.

2. Participant is ≤2 years of age.

3. Participant has not had previous treatment with Zolgensma.

4. Participant has reached full-term gestational age ~~of 40 weeks~~.

5. Prescriber is board certified in one of the following pediatric specialties or subspecialties: neurology, pulmonology, orthopedics, neonatal-perinatal medicine, clinical genetics and genomics, physical medicine and rehabilitation, neuromuscular medicine, or neurodevelopmental disabilities.

6. Participant does not have advanced SMA. (e.g., complete paralysis of limbs and/or permanent ventilator dependence)

7. Prescriber provides documentation of baseline AST, ALT, total bilirubin, prothrombin time, platelet count, and troponin I levels within 30 days of request.

8. Prescriber provides documentation of anti-AAV9 antibody testing. Participants must demonstrate anti-AAV9 antibody titers ≤1:50.

9. Prescriber documents that participant does not have presence of prodrome or resolving viral infection.

10. Prescriber verifies vaccine schedule has been reviewed and modified, if necessary.

11. Systemic corticosteroids equivalent to oral prednisolone dosed at 1mg/kg per day will be initiated one day prior to infusion for a total of 30 days and continued or tapered per prescribing information based on liver function.

12. After 30 days of required systemic-corticosteroid treatment, prescriber provides clinical update including AST, ALT, total bilirubin levels, prothrombin time, platelet count, and troponin I levels.

13. Participant will not be approved for concomitant treatment with nusinersen following Zolgensma infusion and current nusinersen authorizations will be discontinued upon Zolgensma approval. Subsequent approval for administration of nusinersen after Zolgenmsa infusion will be reviewed on a case by case basis.

References

1. 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.
2. Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord*. 2018;28(2):103-115.
3. SMA Foundation. About SMA: Informational Resources. SMA Overview. Website: Available at: http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf. Accessed 5.09.19.
4. Zolgensma [package insert]. Bannockburn, IL: AveXis, Inc.; May, 2019.

5. New AveXis data at AAN showed long-term durability of Zolgensma in patients with spinal muscular atrophy (SMA) Type 1; Novartis Web site; https://www.novartis.com/news/media-releases/new-avexis-data-aan-showed-long-term-durability-zolgensma-patients-spinal-muscular-atrophy-sma-type-1; Published May 7, 2019. Access May 9, 2019.
6. AveXis data reinforce effectiveness of Zolgensma in treating spinal muscular atrophy (SMA) Type 1; Novartis Web site; https://www.novartis.com/news/media-releases/avexis-data-reinforce-effectiveness-zolgensma-treating-spinal-muscular-atrophy-sma-type-1; Published April 16, 2019. Access May 9, 2019.
7. AveXis presented robust data at AAN demonstrating efficacy of Zolgensma in broad spectrum of spinal muscular atrphy (SMA) patients; Novartis Web site; https://www.novartis.com/news/media-releases/avexis-presented-robust-data-aan-demonstrating-efficacy-zolgensma-broad-spectrum-spinal-muscular-atrophy-sma-patients; Published May 5, 2019. Accessed May 9, 2019.