Zolgensma® (onasemnogene abeparvovec-xioi) – New orphan drug approval

- On May 24, 2019, the FDA announced the approval of Novartis/AveXis' Zolgensma (onasemnogene abeparvovec-xioi), 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.

    — The safety and effectiveness of repeat administration of Zolgensma have not been evaluated.
    — The use of Zolgensma in patients with advanced SMA (eg, complete paralysis of limbs, permanent ventilator-dependence) has not been evaluated.

- SMA is a rare genetic disease caused by a mutation in the *SMN1* gene. The gene encodes the SMN protein – a protein found throughout the body, which is critical for the maintenance and function of specialized nerve cells, called motor neurons. If there is not enough functional SMN protein, then the motor neurons die, leading to debilitating and often fatal muscle weakness. The incidence of SMA is approximately 1 in 10,000 live births and it is the leading genetic cause of infant mortality.

    — SMA caused by mutations in the *SMN1* gene is generally classified into several subtypes, based on the age of onset and severity; infantile-onset SMA is the most severe and most common subtype. Children with this condition have problems holding their head up, swallowing and breathing.

- Zolgensma is an adeno-associated viral vector-based gene therapy. Zolgensma is designed to deliver a copy of the gene encoding the human SMN protein.

- The efficacy of Zolgensma in 21 pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene was evaluated in an ongoing single-arm study. Efficacy was established on the basis of survival, and achievement of developmental motor milestones such as sitting without support.

    — As of the March 2019 data cutoff, 19 patients were alive without permanent ventilation and were continuing in the study, while one patient died at age 7.8 months due to disease progression, and one patient withdrew from the study at age 11.9 months. The 19 surviving patients who were continuing in the study ranged in age from 9.4 to 18.5 months.
    — By the data cutoff, 13 of the 19 patients continuing in the study reached 14 months of age without permanent ventilation.
    — In addition, 10 of the 21 patients (47.6%) achieved the ability to sit without support for ≥ 30 seconds between 9.2 and 16.9 months of age and 16 of the 19 patients had not required daily non-invasive ventilator use.

- Zolgensma was also evaluated in a completed single-arm, ascending-dose study in 15 patients with infantile-onset SMA. Three patients were in the low-dose cohort and 12 in a high-dose cohort.

    — By 24 months following Zolgensma infusion, one 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.
    — 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.

- Zolgensma carries a boxed warning for acute serious liver injury.

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- Additional warnings and precautions for Zolgensma use include thrombocytopenia and elevated troponin-I.

- The most common adverse reactions (≥ 5%) with Zolgensma use were elevated aminotransferases and vomiting.

- The recommended dose of Zolgensma is 1.1×10^{14} vector genomes per kilogram (vg/kg) of body weight. Zolgensma should be administered as a single-dose intravenous infusion over 60 minutes.

    — Starting one day prior to Zolgensma infusion, patients should receive systemic corticosteroids equivalent to oral prednisolone at 1 milligram per kilogram of body weight per day (mg/kg/day) for a total of 30 days.
    — Refer to the Zolgensma drug label for additional dosing and administration recommendations.

- Zolgensma will be priced at $2.125 million for a one-time dose.

    — AveXis has announced that they are working closely with payers to offer pay-over-time options up to 5 years and outcomes-based agreements up to 5 years, as well as providing a patient program to support affordability and access.

- Novartis/AveXis' launch plans for Zolgensma are pending. Zolgensma will be provided in a kit containing 2 to 9 vials; vials are provided in 2 fill volumes (either 5.5 mL or 8.3 mL). All vials have a nominal concentration of 2.0×10^{13} vg/mL.