Lenmeldy™ (atidarsagene autotemcel) – New orphan drug approval

- On March 18, 2024, the FDA announced the approval of Orchard Therapeutics' Lenmeldy (atidarsagene autotemcel), for the treatment of children with pre-symptomatic late infantile (PSLI), presymptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD).

- MLD is a debilitating, rare genetic disease affecting the brain and nervous system. It is caused by a deficiency of an enzyme called arylsulfatase A (ARSA), leading to a buildup of sulfatides (fatty substances) in the cells. This buildup causes damage to the central and peripheral nervous system, manifesting with loss of motor and cognitive function and early death.

    - It is estimated that MLD affects one in every 40,000 individuals in the U.S.
    - There is no cure for MLD, and treatment typically focuses on supportive care and symptom management.

- Lenmeldy is a one-time, individualized single-dose infusion made from the patient's own hematopoietic stem cells, which have been genetically modified to include functional copies of the ARSA gene. The stem cells are collected from the patient and modified by adding a functional copy of the ARSA gene. The modified stem cells are transplanted back into the patient where they engraft within the bone marrow. The modified stem cells supply the body with myeloid cells that produce the ARSA enzyme, which helps break down the harmful build-up of sulfatides and may stop the progression of MLD.

    - Prior to treatment, patients must undergo high-dose chemotherapy, a process that removes cells from the bone marrow so they can be replaced with the modified cells in Lenmeldy.

- The efficacy of Lenmeldy was established in two single-arm, open-label clinical studies and in an expanded access program in 37 children with MLD. Children who received treatment with Lenmeldy were compared to untreated children (natural history). The primary endpoint was severe motor impairment-free survival, defined as the interval from birth to the first occurrence of loss of locomotion and loss of sitting without support or death.

    - In children with MLD, treatment with Lenmeldy significantly reduced the risk of severe motor impairment or death compared with untreated children.
    - All children with PSLI MLD who were treated with Lenmeldy were alive at 6 years of age, compared to only 58% of children in the natural history group. At 5 years of age, 71% of treated children were able to walk without assistance. Eighty-five percent of the children treated had normal language and performance IQ scores, which has not been reported in untreated children.
    - In addition, children with PSEJ and ESEJ MLD showed slowing of motor and/or cognitive disease.

- Warnings and precautions for Lenmeldy include thrombosis and thromboembolic events; encephalitis; serious infections; veno-occlusive disease; delayed platelet engraftment; neutrophil engraftment failure; insertional oncogenesis; hypersensitivity reactions; anti-retroviral use; and interference with serology testing.

- The most common non-laboratory adverse reactions (≥ 10%) with Lenmeldy use were febrile neutropenia, stomatitis, respiratory tract infections, rash, device related infections, other viral

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infections, pyrexia, gastroenteritis, and hepatomegaly. The most common laboratory abnormalities were elevated D-dimer, neutropenia, and elevated liver enzymes.

- Lenmeldy is provided as a single dose for infusion containing a suspension of CD34+ cells in one to eight infusion bags. Refer to the Lenmeldy drug label for complete dosing and administration recommendations.

- Orchard Therapeutics' launch plans for Lenmeldy are pending.