Evrysdi™ (risdiplam) – New orphan drug approval

- On August 7, 2020, the FDA announced the approval of Genentech's Evrysdi (risdiplam), for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

- SMA is a hereditary disease that causes weakness and muscle wasting because patients lose lower motor neurons that control movement.

    - It affects approximately one in 10,000 babies.

- Evrysdi is the first oral treatment available for the treatment of SMA. Evrysdi is a survival of motor neuron 2 (SMN2) splicing modifier designed to treat patients with SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency.

- The efficacy of Evrysdi for the treatment of patients with infantile-onset and later-onset SMA was evaluated in two studies. Study 1, part 1 was an open-label study enrolling 21 patients with type 1 SMA (symptom onset between 28 days and 3 months of age). Effectiveness was established based on the ability to sit without support for at least 5 seconds and on the basis of survival without permanent ventilation.

    - Of the patients who were treated with the recommended dosage of Evrysdi 0.2 mg/kg/day, 41% (7/17) were able to sit independently for ≥ 5 seconds after 12 months of treatment.
    - After 12 months of treatment with Evrysdi, 90% (19/21) of patients were alive without permanent ventilation (and reached 15 months of age or older).

- Study 2, part 2 was a double-blind, placebo-controlled study that enrolled 180 non-ambulatory patients with type 2 (71%) or type 3 (29%) SMA. The primary endpoint was the change from baseline to month 12 in the Motor Function Measure 32 (MFM32) score. Key secondary endpoints were the proportion of patients with a 3-point or greater change from baseline to month 12 in the MFM32 total score and the Revised Upper Limb Module (RULM).

    - The least square (LS) mean changed in the primary endpoint was 1.36 for the Evrysdi-treated patients vs. -0.19 for the placebo-control group (Difference: 1.55; 95% CI: 0.30, 2.81; p = 0.0156).
    - The proportion of patients with a change from baseline MFM32 total score of 3 or more at month 12 was 38.3% of the Evrysdi-treated patients vs. 23.7% of the placebo-control group (Odds ratio for overall response: 2.35; 95% CI: 1.01, 5.44; p = 0.0469).
    - The LS mean change from baseline in total score of RULM at month 12 was 1.61 for the Evrysdi-treated patients vs. 0.02 for the placebo-control group (Difference: 1.59; 95% CI: 0.55, 2.62; p = 0.0469).

- The most common adverse reactions (≥ 10% and > control) in later-onset SMA with Evrysdi use were fever, diarrhea, and rash.

- The most common adverse reactions in infantile-onset SMA were similar to those observed in later-onset SMA patients. Additionally, adverse reactions occurring in ≥ 10% were upper respiratory tract infection, pneumonia, constipation, and vomiting.

- The recommended dose of Evrysdi is administered orally once daily. The recommended dosage is determined by age and body weight as follows:

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Age and Body Weight	Recommended Daily Dose
2 months to less than 2 years of age	0.2 mg/kg
2 years of age and older weighing less than 20 kg	0.25 mg/kg
2 years of age and older weighing 20 kg or more	5 mg

  - It is recommended that a healthcare provider discuss with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose.
  - Patients or caregivers should be instructed to prepare the dose using the reusable oral syringe provided.

- Per Roche, the price for Evrysdi is tied to the patient's weight and is capped at $340,000 per year once a patient reaches 44 pounds. For an infant weighing 15 pounds, the average weight of study participants in one of Roche's trials, the annual cost would be less than $100,000.

- Genentech plans to launch Evrysdi within two weeks. Evrysdi will be available as a 60 mg oral powder for constitution.