RXADVANCE
2 Park Central Drive
Southborough, MA 01772

NEW DRUG APPROVAL

Brand Name	EVRYSDI™
Generic Name	risdiplam
Drug Manufacturer	GENENTECH INC

New Drug Approval

FDA Approval Date: August 7, 2020
Review Designation: Orphan
Type of Review: New Drug Application 213535

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Spinal muscular atrophy is a genetic disorder characterized by weakness and wasting (atrophy) in muscles used for movement (skeletal muscles). It is caused by a loss of specialized nerve cells, called motor neurons that control muscle movement. The weakness tends to be more severe in the muscles that are close to the center of the body (proximal) compared to muscles away from the body's center (distal). The muscle weakness usually worsens with age. There are many types of spinal muscular atrophy that are caused by changes in the same genes. The types differ in age of onset and severity of muscle weakness; however, there is overlap between the types.

It affects all racial and ethnic groups. With an estimated incidence of approximately 1 in 10,00-11,00 live births, Spinal Muscular Atrophy (SMA) is the second most common autosomal recessive cause of death in children in the United States. According to a variety of sources, estimated number of patients in the United States is between 10,000 - 25,000.

Efficacy

The efficacy of EVRYSDI™ for the treatment of patients with infantile-onset and later-onset SMA was evaluated in two clinical studies, Study 1 (NCT02913482) and Study 2 (NCT02908685).

The overall findings of these studies support the effectiveness of EVRYSDI™ in SMA patients 2 months of age and older and appear to support the early initiation of treatment with EVRYSDI™.

Infantile-Onset SMA: Study 1 was an open-label, 2-part study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of EVRYSDI™ in patients with Type 1 SMA (symptom onset between 28 days and 3 months of age). In Study 1 Part 1, the median duration of EVRYSDI™ treatment was 14.8 months (range: 0.6 to 26.0), and 19 patients were treated for a minimum duration of 12 months.

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). After a minimum of 23 months of treatment with EVRYSDI™, 81% (17/21) of all patients were alive without permanent ventilation (and reached an age of 28 months or older; median 32 months; range 28 to 45 months).

Later-Onset SMA: Study 2 was a 2-part, multicenter trial to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of EVRYSDI™ in patients diagnosed with SMA Type 2 or Type 3. The primary endpoint in Study 2 Part 2 was the change from baseline to Month 12 in the Motor Function Measure 32 (MFM32) score.

NEW DRUG APPROVAL

The primary analysis on the change from baseline in MFM32 total score at Month 12 showed a clinically meaningful and statistically significant difference between patients treated with EVRYSDI™ and placebo.

Safety

ADVERSE EVENTS

- The most common adverse reactions in later-onset SMA (incidence at least 10% of patients treated with EVRYSDI™ and more frequent than control) 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 with an incidence of at least 10% were upper respiratory tract infection, pneumonia, constipation, and vomiting.

WARNINGS & PRECAUTIONS

None

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Risdiplam is a survival of motor neuron 2 (SMN2) splicing modifier designed to treat patients with spinal muscular atrophy (SMA) caused by mutations in chromosome 5q that lead to SMN protein deficiency. Using in vitro assays and studies in transgenic animal models of SMA, risdiplam was shown to increase exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein in the brain.

Dose & Administration

ADULTS

- 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

PEDIATRICS

The safety and effectiveness of EVRYSDI™ in pediatric patients 2 months of age and older have been established. Safety and effectiveness in pediatric patients below the age of 2 months have not been established.

GERIATRICS

Clinical studies of EVRYSDI™ did not include patients aged 65 years and over to determine whether they respond differently from younger patients.

RENAL IMPAIRMENT

Renal impairment is not expected to alter the exposures to risdiplam.

HEPATIC IMPAIRMENT

The safety and efficacy of EVRYSDI™ in patients with hepatic impairment have not been studied.

NEW DRUG APPROVAL

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

60 mg of risdiplam as a powder for constitution to provide 0.75 mg/mL solution.