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In Brief: Risdiplam *(Evrysdi)* for Spinal Muscular Atrophy

IN BRIEF

Risdiplam *(Evrysdi)* for Spinal Muscular Atrophy

Risdiplam (*Evrysdi* – Genentech), a survival of motor neuron 2 (SMN2) splicing modifier, has been approved by the FDA for oral treatment of spinal muscular atrophy (SMA) in patients ≥2 months old. It is the first oral drug to be approved in the US for treatment of SMA; nusinersen *(Spinraza),* an intrathecally administered SMN2-directed antisense oligonucleotide, and onasemnogene abeparvovec *(Zolgensma)*, an IV adeno-associated virus vector-based gene therapy, were approved earlier.[1,2]

Pronunciation Key	
Risdiplam: ris dip' lam	***Evrysdi*:** ev riz' dee

THE DISORDER — SMA is an autosomal recessive disorder in which degeneration of alpha motor neurons in the anterior horn cells of the spinal cord leads to muscle weakness and atrophy. It occurs in about one in every 10,000 births.[3] Most cases of SMA are caused by a homozygous deletion or mutation in the 5q13 SMN1 gene, which leads to SMN protein deficiency. The SMN2 gene also codes for SMN protein, but exon 7 is excluded during splicing, which results in low levels of functional SMN protein; the severity of disease is inversely correlated with the SMN2 copy number.[4]

MECHANISM OF ACTION — Risdiplam is an SMN2 splicing modifier. Like nusinersen, it acts by increasing exon 7 inclusion in SMN2 messenger RNA transcripts, which increases the gene's production of functional SMN protein in the CNS and peripheral tissues.[5]

CLINICAL STUDIES — FDA approval of risdiplam was based on the results of two clinical trials: an open-label trial (FIREFISH) in infants 2-7 months old (infantile-onset; type 1 SMA) and a randomized, double-blind trial (SUNFISH) in patients 2-25 years old (later-onset SMA; type 2 or 3 SMA). Both trials consisted of two parts: a dose-finding study and an efficacy study.

In FIREFISH part 1 (results of part 2 have not been published to date), 4 infants were treated with a low dose (final dose of 0.08 mg/kg) of risdiplam and 17 were treated with the recommended dose (final dose of 0.2 mg/kg). Median SMN protein concentrations had increased from baseline by a median of 3.0 times in the low-dose group and by 1.9 times in the higher-dose group at 12 months. Seven patients in the higher-dose group and none in the low-dose group were able to sit without support for at least 5 seconds at 12 months.[6] Among infants treated with risdiplam for ≥12 months, 81% (17 out of 21) were alive without the need for permanent ventilation and reached ≥28 months of age.

In SUNFISH part 2, 180 non-ambulatory patients were randomized to receive risdiplam (at the FDA-approved dosage for age and weight) or placebo. At 12 months, significant improvements in motor function, including an increased level of independence in activities of daily living, occurred in more patients taking risdiplam than in those taking placebo. The change from baseline at 12 months in the motor function measure 32 (MFM32) score, with higher scores indicating greater motor function, was 1.36 with risdiplam and -0.19 with placebo, a statistically significant difference.[7]

Two open-label trials, one in patients 6-60 years old with SMA (JEWELFISH) and one in infants ≤6 weeks old with SMA (RAINBOWFISH), are ongoing.

ADVERSE EFFECTS — The most common adverse effects of risdiplam (occurring in ≥5% of patients and at higher rates than with placebo in SUNFISH part 2) were fever, diarrhea, rash, mouth and aphthous ulcers, arthralgia, and urinary tract infection. Irreversible

retinal degeneration was observed in animals exposed to higher concentrations of the drug than those used in FIREFISH and SUNFISH.

DOSAGE, ADMINISTRATION, AND COST — Risdiplam should be administered orally or via nasogastric or gastrostomy tube once daily after a meal. The recommended dosage is 0.2 mg/kg in patients 2 months-<2 years old, 0.25 mg/kg in those ≥2 years old weighing <20 kg, and 5 mg in those ≥2 years old weighing ≥20 kg. The cost of one year's treatment with *Evrysdi* is $335,100.[8] ■

1. Nusinersen (Spinraza) for spinal muscular atrophy. Med Lett Drugs Ther 2017; 59:50.
2. Zolgensma – one-time gene therapy for spinal muscular atrophy. Med Lett Drugs Ther 2019; 61:113.
3. EA Sugarman et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet 2012; 20:27.
4. MA Farrar et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol 2017; 81:355.
5. A Poirier et al. Risdiplam distributes and increases SMN protein in both the central nervous system and peripheral organs. Pharmacol Res Perspect 2018; 6:e00447.
6. G Baranello et al. Risdiplam in type 1 spinal muscular atrophy. N Engl J Med 2021; 384:915.
7. E Mercuri et al. SUNFISH part 2: efficacy and safety of risdiplam (RG7916) in patients with type 2 or non-ambulant type 3 spinal muscular atrophy (SMA). Neurology 2020; 94(15 Suppl):1260.
8. Cost for a patient ≥2 years old weighing ≥20 kg. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. July 5, 2021. Reprinted with permission by First Databank, Inc. All rights reserved. ©2021. www.fdbhealth.com/drug-pricing-policy.