New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Evrysdi™ (risdiplam) [Genentech]**
Dosage Formulations:	60 mg/80 mL (0.75 mg/mL) oral solution
FDA Approval Date: **FDB File Date:**	FDA: August 7, 2020 FDB: August 16, 2020
Indication:	For the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older
Mechanism of Action:	Survival of motor neuron 2 (SMN2)-directed RNA splicing modifier. Risdiplam increases exon 7 inclusion in SMN2 messenger ribonucleic acid transcripts and production of full-length SMN protein in the brain.

Dose/ Administration:	• Dosed orally once daily using the provided reusable syringe at approximately the same time each day:
	  ○ Patients aged 2 months to < 2 years: 0.2 mg/kg
	  ○ Patients aged 2 years and older with a weight < 20 kg: 0.25 mg/kg
	  ○ Patients aged 2 years and older with a weight ≥ 20 kg: 5 mg
	• Must be taken immediately after being drawn up and should be discarded if not taken within 5 minutes.
	• Can be administered via nasogastric or gastrostomy tube if necessary.
	• Cannot be mixed with food, formula or milk – administration should occur after a meal or breastfeeding.
	• Must be reconstituted by a pharmacist prior to dispensing, discarded after 64 days, and stored in the refrigerator.

Drug Clinical Highlights:	• FDA granted Orphan Drug designation
	• No documented contraindications
	• The most common adverse reactions reported (≥ 10%) were fever, diarrhea, and rash in later-onset SMA while upper respiratory tract infection, pneumonia, constipation, and vomiting were reported in infantile-onset SMA.
	• Drug-drug interactions include concomitant administration with drugs that are substrates of multidrug and toxin extrusion (MATE) transporters (i.e., metformin, cimetidine, acyclovir) – risdiplam may increase plasma concentrations of MATE transporters.
	• Avoid use in patients with hepatic impairment as risdiplam is predominantly metabolized in the liver – safety and efficacy studies in hepatic impairment have not be completed.
	• Avoid use in pregnancy – pregnancy tests and effective contraception are recommended for females of reproductive potential prior to initiation and for at least one month after discontinuation.
	• Consider risk vs. benefit with use of risdiplam in male patients as fertility may be compromised – consider sperm preservation prior to treatment.
	• Strawberry flavored
	• Available for home delivery through Accredo Health Group, Inc. specialty pharmacy
	• FIREFISH Clinical Trial (NCT02913482): open-label, 2-part trial in patients aged 1 to 7 months (N=21) with infantile-onset SMA (Type 1)
	  ○ Part 1: dose finding, safety, tolerability, movement/action of drug in body
	  ○ Part 2: efficacy and safety
	  ○ Patients were enrolled in one of two dosage cohorts. Patients in the higher-dosage cohort had their dose adjusted to the recommended 0.2 mg/kg/day before 12 months of treatment, while patients in the low-dosage cohort did not.
	  ○ Efficacy was based on the ability to sit without support for at least 5 seconds and the basis of survival without permanent ventilation.
	  ○ After the duration of 12 months of treatment:

        - 41% (7/17) of the patients treated with the recommended dosage were able to sit independently for 5 seconds.
        - 90% (19/21) of patients were alive without permanent ventilation at the end of treatment.
    - After a minimum of 23 months of treatment, 81% of patients (17/21) were alive without permanent ventilation.
- SUNFISH Clinical Trial (NCT02908685): randomized (2:1), double-blind, placebo-controlled, 2-part trial in patients aged 2 to 25 years (N=180) with later-onset SMA (Type 2 and 3)
    - Part 1: dose finding, safety, tolerability, movement/action of drug in body
    - Part 2: efficacy and safety
    - Inclusion Criteria:
        - Confirmed diagnosis of 5q-autosomal recessive SMA
        - Negative pregnancy test at screening
        - Type 2 or 3 SMA non-ambulant
        - Revised Upper Limb Module (RULM) entry item A greater than or equal to 2
        - Ability to sit independently
    - Exclusion Criteria:
        - Concurrent or previous administration of SMN2-targeting antisense oligonucleotides, SMN2 splicing modifier or gene therapy
        - Patients requiring invasive ventilation or tracheostomy
    - Patients received the recommended dosage of 0.2 mg/kg/day

	SUNFISH	
Primary Endpoint of Part 2	**Evrysdi (N=120)**	**Placebo (N=60)**
Change from baseline in total MFM-32 score at month 12, LS means (95% CI)	1.36 (0.61, 2.11)	-0.19 (-1.22, 0.84)
Difference from placebo, estimate (95% CI) p-value	1.55 (0.30, 2.81) 0.0156	

    - MFM-32: Motor Function Measure 32 – evaluates 32 different motor functions (with 3 questions each) such as head support, hip and knee flexion, upper limb function, sitting, standing, finger and wrist movement, walking, running and hopping – the higher the score, the less impairment.
    - There was a clinically and statistically significant difference in those treated with Evrysdi vs. those receiving placebo.
- JEWELFISH Clinical Trial
    - Non-naïve patients with SMA
    - Aged 6 months to 60 years
    - Safety, tolerability, movement/action of drug in body
    - Recruitment complete – estimated study completion Jan 2022
- RAINBOWFISH Clinical Trial
    - Pre-symptomatic SMA
    - Aged birth to 6 weeks
    - Efficacy and safety
    - Ongoing (recruitment) – estimated study completion June 2021

Disease State Clinical Highlights:

- SMA is a rare, genetic neuromuscular disease with the most severe cases affecting infants and young children.
- In the U.S. SMA incidence is approximately one in 11,000 live births or about 500 new SMA cases per year.
- Estimated prevalence in the U.S. is 10,000 to 25,000 patients.
- The most common cause of SMA is the homozygous deletion or deletion and mutation of the alleles of the survival motor neuron 1 gene on chromosome 5q.

- SMN1 creates SMN protein, a protein essential for motor neuron development. Although the SMN2 gene also produces SMN protein, only a small amount of the protein it creates is functional. While the number of SMN2 copies modulates the severity of SMA, patients without SMN1 have an insufficient level of SMN protein regardless of the number of SMN2 copies.

Clinical Classification of SMA					
SMA Type	**Age of Onset**	**Highest Achieved Motor Function**	**Natural Age of Death**	**Typical Number of SMN2 Copies**	**Incidence**
0	Prenatal/Fetal	None	< 6 months	1	Very Rare
I	< 6 months	Sit with support only	< 2 years	1-3	60%
II	6-18 months	Sit independently	> 2 years	2-3	20-30%
III	> 18 months	Walk independently	Adulthood	3-4	10-20%
IV	Adulthood (20-30 years)	Walk through adulthood	Adulthood	≥4	Very Rare

Price Per Unit (WAC):

- $139.63/mL ($11,170.43 per 80 mL bottle)
- Max dose of 5 mg/day: $27,926/month or $339,766/year

Therapeutic Alternatives:

	Evrysdi	**Spinraza®**	**Zolgensma®**
MOA	Survival of motor neuron 2 (SMN2)-directed RNA splicing modifier	An antisense oligonucleotide that targets SMN2 so that it creates more functional SMN protein	Recombinant AAV9-based gene therapy designed to deliver a copy of the gene encoding the human SMN protein (SMN1)
Dosing	Orally once a day	Intrathecal injection with four loading doses (day 0,14, 28, 63) and maintenance doses every four months thereafter	Single-dose IV infusion given over 60 minutes
FDA Approved Age	2 months and older	All ages	< 2 years
Cost	$139.63/mL ($11,170.43 per 80mL bottle) OR $339,766 per year	$25,500/mL ($127,500/5mL vial) OR $382,500 per year	$2,125,000 per lifetime

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Prescribed by or in consultation with a neurologist or other specialist within the treated disease state **AND**
- Participant aged 2 months and older **AND**
- Documentation of a confirmed diagnosis of 5q-autosomal recessive spinal muscular atrophy type 1, 2 or 3 (ICD10 G12.0, G12.1) including genetic tests:
  - Homozygous SMN1 gene deletion or mutation **OR**
  - Compound heterozygous SMN1 gene mutation **AND**
- Sufficient number of copies of SMN2 gene defined as one of the following (either 2a or 2b) genetic tests demonstrating:
  - ≥ 2 copies of SMN2 gene **AND**
  - Documentation of age of onset of symptoms **AND**
- Documentation of clinical baseline assessments received:

	○ For participants aged < 3 years: Hammersmith Infant Neurological Exam-Part 2 (HINE-2) **OR** ○ For participants aged ≥ 3 years: Hammersmith Functional Motor Scale Expanded (HFMSE) **AND** ○ Motor Function Measure 32 (MFM-32) **OR** ○ For ambulatory patients: 6 Minute Walk Test (6MWT) **OR** ○ For non-ambulatory patients: Revised Upper Limb Module (RULM) Score **AND** • Participant is currently not pregnant **AND** • Female participants must utilize concurrent birth control methods during and for 1-month post-treatment **AND** • Participant does not require invasive ventilation or tracheostomy **AND** • Participant does not have hepatic impairment **AND** • Participant lacks concurrent administration of MATE transporters, Spinraza or Zolgensma **AND** • Dosing limits: 3 bottles per month/ max of 5 mg per day • Initial therapy approved for 3 months <u>Continuation of Therapy:</u> • Documented compliance on current therapy regimen **AND** • Documentation of benefit from therapy: ○ Improvement or maintenance of functional status from baseline functional tests (HFMSE or HINE-2, pulmonary status, and 6MWT or RULM) **OR** ○ Achievement and maintenance of new motor milestones from pretreatment baseline functional tests (HFMSE or HINE-2 and Pulmonary status) **OR** ○ Less than expected decline in functional ability or symptoms of disease as described by at least 1 of the following: ▪ HFMSE: at least 3 point increase in score from pretreatment baseline **OR** ▪ HINE-2 demonstrates: • Patient has demonstrated improvement in more categories than decline **AND** • At least 2 points (or maximum score) in ability to kick **OR** • At least 1 point in any other HINE milestone (head control, rolling, sitting, crawling, etc.) **OR** ▪ MFM-32: at least 1 point increase in score from pretreatment baseline **OR** ▪ For ambulatory patients 6MWT demonstrates at least a 30-meter increase from pretreatment baseline **OR** ▪ For non-ambulatory patients RULM demonstrates at least 2 point increase in score from the pretreatment baseline **Additional Provider Diagnostic/Monitoring Criteria, if desired:** • Consider risk vs. benefit with use of risdiplam in male patients as fertility may be compromised – consider sperm preservation prior to treatment.
Implication to State Medicaid Program:	• LOE: 5.11.2035 • Evrysdi and Spinraza will be competitors, as they have similar mechanisms of action and there is currently no clinical data justifying concurrent use of these agents. • The JEWELFISH clinical trial is assessing the safety and efficacy of concurrent use of Evrysdi and Zolgensma. If this trial shows clinical benefit in using both agents, budget impacts will be significant.

<u>References:</u>

1. Evrysdi [package insert]. South San Francisco, CA: Genentech Inc: August 2020.
2. IPD Analytics Rx Insights_New Drug Approval Review_Evrysdi. August 2020.
3. Zolgensma [package insert]. Bannockburn, IL: AveXis Inc: May 2019.
4. Spinraza [package insert]. Cambridge, MA. Biogen: June 2020.
5. E. Mercuri et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscular Disorders 28 (2018) 103–115. https://doi.org/10.1016/j.nmd.2017.11.005
6. RS Finkel et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscular Disorders 28 (2018) 197–207. https://doi.org/10.1016/j.nmd.2017.11.004