RXADVANCE
2 Park Central Drive
Southborough, MA 01772

Clinical Policy Title:	risdiplam
Policy Number:	RxA.663
Drug(s) Applied:	Evrysdi™
Original Policy Date:	10/13/2020
Last Review Date:	12/7/2020
Line of Business Policy Applies to:	All lines of business

Background

Evrysdi™ is a survival of motor neuron 2 (SMN2) splicing modifier indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age or older.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
Evrysdi™ (risdiplam)	SMA	Taken orally once daily; recommended dose determined by age and body weight. • 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	5 mg/daily

Dosage Forms

- Oral Solution: 60 mg of risdiplam as a powder for constitution to provide 0.75 mg/mL solution

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. Spinal Muscular Atrophy (must meet all):

1. Patient has confirmed diagnosis of 5q-autosomal recessive type 1, 2, or 3 SMA;
2. Patient is 2 months of age or older;
3. Evrysdi is prescribed by or in consultation with a neurologist specializing in neuromuscular disorders;
4. Patient does not require invasive ventilation or tracheostomy;
5. Patient is symptomatic at the time of request;
6. Patient is not receiving concurrent treatment with Spinraza or Zolgensma; and
7. Dose does not exceed 5 mg daily.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

II. Continued Therapy Approval

A. Spinal Muscular Atrophy (must meet all):

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy (i.e. clinically meaningful improvement in motor function or documentation of disease stabilization in normal motor decline);
3. Dose does not exceed 5 mg daily.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
SMN2: Survival of motor neuron 2
SMA: Spinal Muscular Atrophy

APPENDIX B: Therapeutic Alternatives

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Spinraza ® (nusinersen)	7.5 mg -15 mg PO once daily	15 mg/day
Zolgensma ® (onasemnogene abeparvovec-xioi)	50 mg PO TID	150 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Until the entrance of Spinraza to the market in 2016, the treatment of SMA consisted primarily of supportive therapies. Spinraza was the first FDA-approved pharmacologic treatment that addressed the underlying cause of SMA. Spinraza is an antisense oligonucleotide (ASO). Antisense oligonucleotides were found to be effective in SMA by modulating the splicing of SMN transcripts, and Spinraza specifically was found to alter SMN2 splicing by inhibiting splicing factors. This action increases integration of exon 7 in the SMN2 messenger ribonucleic acid (mRNA) transcripts, ultimately leading to an increase in production of full-length SMN protein. This increase in SMN protein by route of the SMN2 gene can partially compensate for the defective SMN1 gene. Spinraza is indicated for the treatment of adult and pediatric SMA patients and is administered intrathecally every 4 months after a loading-dose phase. In May 2019, a novel gene therapy was approved for the treatment of SMA. Zolgensma is a recombinant adenoassociated virus vector 9 (AAV9) that delivers a copy of the SMN1 gene to the patient, resulting in cell transduction and expression of full-length SMN protein. As opposed to the indefinite administration of Spinraza, Zolgensma offers a onetime treatment option via a 60-minute intravenous infusion. Repeat administration of Zolgensma has not been evaluated. Zolgensma's indication is limited to the treatment of pediatric patients less than 2 years of age.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None

- Boxed Warning(s):
  - None

APPENDIX D: General Information

Spinal muscular atrophy (SMA) is a genetic, autosomal-recessive neuromuscular disorder caused by a defect in the survival of motor neuron 1 (SMN1) gene. The SMN1 gene is responsible for producing the majority of survival motor neuron (SMN) protein, which plays a critical role in the development and survival of motor neurons. This defect in SMN1 causes degeneration in the spinal cord and lower brainstem, which manifests as progressive muscle weakness and eventual loss of motor function. The phenotypic expression of the mutation is dependent on multiple variables, including the number of copies of survival of motor neuron 2 (SMN2). The number of SMN2 copies is an important variable that affects the severity of the disease, as SMN2 also produces the SMN protein to a lesser extent and can partially compensate for the SMN deficiency. Spinal muscular atrophy is classified into 5 types (types 0 to 4) and are reviewed in the table below.

SMA Classification

SMA Type	*SMN2* Copies	Onset	Motor Development	Prognosis	Natural Age of Death
0	1	In utero	None (unable to sit or roll)	Respiratory insufficiency at birth; death occurs within weeks after birth	<6 months
1	2	<6 months	Unable to sit or roll unassisted	Death/ventilation by 2 years of age	<2 years
2	3, 4	6–18 months	Sit independently, but unable to stand or walk unassisted	Survival into adulthood	>2 years (70% alive at 25 years)
3	3, 4	Early childhood to early adulthood	Stand and walk independently, but loss of function as disease progresses	Normal life span (typically)	Adulthood
4	4–8	Adult, usually after age 30 years	Ambulatory during adulthood, but may experience mild muscle weakness	Normal life span	Adulthood

Source: Kolb SJ, Kissel JT. Spinal muscular atrophy. *Neurol Clin*. 2015;33(4):831-846.

References

1. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2020. Accessed with subscription at: http://www.clinicalkey.com. Updated July 10, 2020. Accessed September 27, 2020.
2. Evrysdi™ (risdiplam), for oral solution prescribing information (per FDB). South San Francisco, CA; Genentech Inc., 2020, August. Accessed October 12, 2020.
3. IPD Analytics. Accessed with subscription at: http://secure.ipdanalytics.com. Accessed October 15, 2020.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	10/15/2020	12/07/2020