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Subject: Risdiplam (Evrysdi™)

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Dosage/ Administration | Position Statement | Billing/Coding | Reimbursement | Program Exceptions | Definitions

Related Guidelines | Other | References | Updates

DESCRIPTION:

Spinal muscular atrophy (SMA) is a group of genetic disorders characterized by a loss of motor neurons. While there are numerous gene mutations that can cause the different forms of SMA, 95% of cases result from a homozygous deletion or mutation in the 5q13 survival of motor neuron (SMN1) gene. This deficiency results in degeneration of motor neurons causing muscle atrophy, particularly in the limbs and the muscles that control the mouth, throat and respiration. A second gene, SMN2, is nearly identical to SMN1 but does not produce much functional (i.e., full length, stable) SMN protein. While there is generally one SMN1 per chromosome, there is a variable number of SMN2 gene copies.

The severity of SMA (an autosomal recessive disorder) is highly variable and correlates mainly with the number of SMN2 gene copies. The clinical features can be classified based on the age of onset and maximum motor function (table 1).

Table 1. SMA Classification

Type	Age of onset	Highest Function	Natural Age of Death	Copies of SMN2
0	Prenatal	Respiratory failure	< 1 month	1
I (Werdnig-Hoffman disease)	0-6 months	Never sit	< 2 years	2
II (Dubowitz disease)	< 18 months	Never stand	> 2 years	3, 4
III (Kugelberg-Welander disease)	18 months-21 years	Stand or ambulatory	Adult	3, 4
IV (adult onset)	> 21 years	Ambulatory	Adult	4-8

The incidence of SMA is approximately 1 in 11,000 live births and it is reported to be the leading genetic cause of infant death. Carrier frequencies are estimated at 1 in 40 to 1 in 60. SMA can be diagnosed by DNA analysis detection of SMN1 deletion in both SMN1 alleles. This is approximately 95% sensitive (100% specific) for patients with clinical features suspicious for SMA.

There is no known cure for SMA. Treatment is designed to address the primary and secondary effects of muscle weakness and includes management of pulmonary complications, nutritional and gastrointestinal support, orthopedic care, rehabilitative interventions, and end-of-life care.

Risdiplam (Evrysdi) was approved by the U.S. Food and Drug Administration (FDA) in August 2020 for the treatment of spinal muscular atrophy in patients 2 months of age and older. Risdiplam is a SMN2 splicing modifier. The safety and efficacy of risdiplam were evaluated in two clinical trials: FIREFISH (NCT02913482) and SUNFISH (NCT02908685). Both FIREFISH and SUNFISH are ongoing and results are pending publication. Two additional clinical trials (JEWELFISH, RAINBOWFISH) are ongoing and are evaluating risdiplam in non-naïve patients or in patients with pre-symptomatic SMA.

FIREFISH was an open-label, 2-part study in 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 (as measured by Item 22 of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) gross motor scale) and on the basis of survival without permanent ventilation. Permanent ventilation was defined as requiring a tracheostomy or more than 21 consecutive days of either non-invasive ventilation (≥ 16 hours per day) or intubation, in the absence of an acute reversible event.

The median age of onset of clinical signs and symptoms of Type 1 SMA in patients enrolled in Part 1 was 2.0 months (range: 0.9 to 3.0); 71% of patients were female, 81% were Caucasian, and 19% were Asian. The median age at enrollment was 6.7 months (range: 3.3 to 6.9), and the median time between onset of symptoms and first dose was 4.0 months (range: 2.0 to 5.8). All patients had genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene, and two SMN2 gene copies. In Part 1, the median duration of risdiplam treatment was 14.8 months (range: 0.6 to 26.0), and 19 patients were treated for a minimum duration of 12 months.

Of the patients who were treated with the recommended dosage of 0.2 mg/kg/day, 41% (7/17) were able to sit independently for ≥ 5 seconds (BSID-III, Item 22) after 12 months of treatment. After 12 months of treatment with, 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, 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).

SUNFISH was a 2-part, multicenter trial in patients diagnosed with SMA Type 2 or Type 3. Part 1 was dose-finding and exploratory in 51 patients (14% ambulatory), while part 2 was a randomized, double-blind, placebo-controlled trial. The primary endpoint was the change from baseline to Month 12 in the Motor Function Measure 32 (MFM32) score. A key secondary endpoint was the proportion of patients with a 3-point or greater change from baseline to Month 12 in the MFM32 total score. The MFM32 measures motor function abilities that relate to daily functions. The total MFM32 score is expressed as a percentage (range: 0 to 100) of the maximum possible score, with higher scores indicating greater motor function. Another key secondary endpoint was the Revised Upper Limb Module (RULM). The RULM is a tool used to assess motor performance of the upper limb in SMA patients. It tests proximal and distal motor functions of the arm. The total score ranges from 0 (all the items cannot be performed) to 37 (all the activities are achieved fully without any compensatory maneuvers).

Part 2 enrolled 180 non-ambulatory patients with Type 2 (71%) or Type 3 (29%) SMA. Patients were randomized 2:1 to receive risdiplam or placebo. Randomization was stratified by age group (2 to 5, 6 to 11, 12 to 17, or 18 to 25 years of age). The median age of patients at the start of treatment was 9.0 years (range 2 to 25), and the median time between onset of initial SMA symptoms and first treatment was 102.6 months (range 1 to 275). Of the 180 patients included in the trial, 51% were female, 67% were Caucasian, and 19% were Asian. At baseline, 67% of patients had scoliosis (32% of them with severe scoliosis). Patients had a mean baseline MFM32 score of 46.1, and RULM score of 20.1. Overall baseline demographic characteristics were reasonably balanced between the treatment groups except for scoliosis (63% in the risdiplam arm vs. 73% in the placebo group).

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 risdiplam and placebo. The results of the primary analysis and key secondary endpoints are shown in the table below:

Endpoint	Risdiplam arm (n=120)	Placebo arm (n=60)
Change from baseline in total MFM32 score at Month 12, LS means (95% CI) [1,2,3]	1,2,3 1.36 (0.61, 2.11)	-0.19 (-1.22, 0.84)
Proportion of patients with a change from baseline MFM32 total score of 3 or more at Month 12 (95% CI) [2,3]	38.3% (28.9, 47.6)	23.7% (12.0, 35.4)
Change from baseline in total score of RULM at Month 12, LS means (95% CI) [1,4]	1.61 (1.00, 2.22)	0.02 (-0.83, 0.87)

Notes:

1. The Mixed Model Repeated Measure (MMRM) analysis included the change from baseline total score as the dependent variable and as independent variables the baseline total score, treatment group, time, treatment-by-time interaction, and the randomization stratification variable of age group (2 to 5, 6 to 11, 12 to 17, 18 to 25).

2. The MFM total score was calculated according to the user manual, expressed as a percentage of the maximum score possible for the scale (i.e., sum of the 32 item scores divided by 96 and multiplied by 100).

3. Based on the missing data rule for MFM32, 6 patients were excluded from the analysis (risdiplam, n = 115; placebo control n = 59).

4. Based on the missing data rule for RULM, 3 patients were excluded from the analysis (risdiplam, n = 119; placebo control n = 58).

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore,

coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of risdiplam **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with spinal muscular atrophy (SMA) type I, II, or III
2. Member's diagnosis has been confirmed by either of the following:
    a. Homozygous deletion of SMN1 gene exon 7 (with or without deletion of exon 8) – laboratory documentation must be provided
    b. Single copy of SMN1 with sequencing of the coding region to confirm a mutation rendering a homozygous dysfunction of the gene – laboratory documentation must be provided
3. Member meets one of the following:
    a. Member has less than four copies of SMN2 – laboratory documentation must be provided
    b. Member has four copies of SMN2 and developed SMA-associated symptoms prior to 21 years of age – laboratory documentation and documentation from the medical record must be provided
4. Member's baseline motor ability prior to or shortly after initial treatment with risdiplam is established with one of the following exams:
    a. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
    b. Hammersmith Infant Neurological Exam Part 2 (HINE-2)
    c. Hammersmith Functional Motor Scale Expanded (HFMSE)
    d. Revised Upper Limb Module (RULM) Test

    NOTE: Submission of baseline motor ability is not required for initial approval, but will be required upon request for continuation of therapy
5. Member is not dependent on invasive ventilation (tracheostomy)
6. Member is not dependent on respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in absence of an acute reversible illness, excluding perioperative ventilation
7. Treatment is prescribed by or in consultation with a board certified (or board eligible) neurologist
8. Member will not receive treatment with nusinersen (Spinraza)

    NOTE: Member's medical record will be reviewed and any current authorizations for nusinersen will be terminated upon risdiplam approval
9. **ONE** of the following:
    a. Member has not previously received gene therapy (including Zolgensma) for SMA

b. Member previously received gene therapy **AND** was unable to maintain beneficial response in SMA-associated symptoms – documentation from the medical record must be provided

10. Member is not concurrently enrolled in a clinical trial to receive an experimental therapy for SMA
11. Dose does not exceed 5 mg

Approval duration: 6 months

Continuation of risdiplam **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue in the past two years for treatment of spinal muscular atrophy (SMA), **OR** the member has previously met all indication-specific initiation criteria
2. Member's diagnosis has been confirmed by either of the following:
    a. Homozygous deletion of SMN1 gene exon 7 (with or without deletion of exon 8) – laboratory documentation must be provided
    b. Single copy of SMN1 with sequencing of the coding region to confirm a mutation rendering a homozygous dysfunction of the gene – laboratory documentation must be provided
3. Member is not dependent on invasive ventilation (tracheostomy)
4. Member is not dependent on respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in absence of an acute reversible illness, excluding perioperative ventilation
5. Member has improved or maintained a previous improvement in motor ability as demonstrated by recent (within 90 days of request) results from one of the following exams – documentation from the medical record must be provided
    a. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
    b. Hammersmith Infant Neurological Exam Part 2 (HINE-2)
    c. Hammersmith Functional Motor Scale Expanded (HFMSE)
    d. Revised Upper Limb Module (RULM) Test
6. Member is not receiving treatment with nusinersen (Spinraza)

    NOTE: Member's medical record will be reviewed and any current authorizations for nusinersen will be terminated upon risdiplam approval
7. Treatment is prescribed by or in consultation with a board certified (or board eligible) neurologist
8. Dose does not exceed 5 mg

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Dose is administered orally once daily after a meal at approximately the same time each day
- Recommended dose is determined by age and body weight:
    - Less than 2 months of age: 0.15 mg/kg
    - 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

Dose Adjustments

- None

Drug Availability

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

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- None

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, not otherwise specified

ICD-10 Diagnosis Codes That Support Medical Necessity

G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]
G12.1	Other inherited spinal muscular atrophy
G12.8	Other spinal muscular atrophies and related syndromes
G12.9	Spinal muscular atrophy, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 12/11/24.

GUIDELINE UPDATE INFORMATION:

09/15/20	New Medical Coverage Guideline.
04/15/21	Review and revision to guideline; updated position statement and references.
01/15/22	Review and revision to guideline; updated references.
01/15/23	Review and revision to guideline; updated position statement and references.
01/15/24	Review and revision to guideline; Updated references.
07/15/24	Revision to guideline; updated dosage/administration
01/15/25	Review and revision to guideline; Updated references.