risdiplam (Evrysdi®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO208

Description

Risdiplam (Evrysdi) is an orally administered survival of motor neuron 2 (SMN2) splicing modifier.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
risdiplam (Evrysdi)	Spinal Muscular Atrophy	60 mg/80 mL (0.75 mg/mL) solution	240 mL/30 days

Initial Evaluation

I. **Risdiplam (Evrysdi)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a neuromuscular specialist; **AND**
   B. Provider attestation that nusinersen (Spinraza) will not be used concurrently with risdiplam (Evrysdi); **AND**
   C. A diagnosis of **5q spinal muscular atrophy (SMA)** when the following are met:
      1. Homozygous deletion of the *SMN1* gene or dysfunctional mutation of the *SMN1* gene; **AND**
      2. Provider attests member does not require invasive ventilation or tracheostomy; **AND**
      3. Provider attestation of ONE of the following:
         i. The member has not had treatment with onasemnogene abeparvovec-xioi (Zolgensma); **OR**
         ii. The member has been treated with onasemnogene abeparvovec-xioi (Zolgensma); **AND**
            a. There has been clinical deterioration or poor response to treatment; **AND**
      4. Member must have ONE of the following SMA phenotypes:
         i. Pre-symptomatic SMA with two or three copies of the *SMN2* gene; **OR**
         ii. SMA Type I; **OR**
         iii. SMA II with symptomatic disease (e.g., impaired motor function and/or delayed motor milestones); **OR**

iv. SMA III with symptomatic disease (e.g., impaired motor function and/or delayed motor milestones); **AND**

5. Baseline documentation of at least ONE of the following motor function/milestone measures:
   i. Members less than two years of age:
      a. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), OR Hammersmith Infant Neurologic Exam (HINE); **OR**
   ii. Members two years of age or older:
      a. Motor Function Measure 32 (MFM32), Revised Upper Limb Module (RULM), Hammersmith Functional Motor Scale Expanded (HFMSE), OR Six-Minute Walk Test (6MWT).

II. Risdiplam (Evrysdi) is considered investigational when used for all other conditions, including but not limited to:
   A. Use in members with Type IV SMA
   B. Used in combination with nusinersen (Spinraza)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has responded to therapy, defined as stability or improvement in net motor function/milestones, compared to pretreatment baseline as exemplified by at least ONE of the following:
   A. Members less than two years of age:
      1. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Hammersmith Infant Neurologic Exam (HINE), OR Bayley Scales of Infant Development–Third Edition (BSID-III) Item 22; **OR**
   B. Members two years of age or older:
      1. Motor Function Measure 32 (MFM32), Revised Upper Limb Module (RULM), Hammersmith Functional Motor Scale Expanded (HFMSE), OR Six-Minute Walk Test (6MWT); **OR**
   C. Provider attests that member has had a slowed rate of decline in the aforementioned measures compared to pretreatment rate.

Supporting Evidence

I. Spinal Muscular atrophy (SMA) is an autosomal recessive genetic disorder caused by mutations in chromosome 5q that lead to survival motor neuron (*SMN*) protein deficiencies. *SMN* protein from the *SMN1* gene, located on chromosome 5, is expressed in all cells and is required for life. In order to develop SMA, an individual must inherit two faulty *SMN1* genes, one from each parent; however, the majority of mutations responsible for 5q-SMA are either deletions or gene conversions.

II. SMA subtype/phenotype is determined primarily by motor milestone attained. Risdiplam (Evrysdi) is FDA approved to treat pediatric and adult patients with pre-symptomatic or symptomatic SMA. Pre-symptomatic patients do not present with symptoms of SMA but have been genetically diagnosed in utero or via newborn screening. SMA trials have shown that patients who begin treatment earlier may have more favorable outcomes.

III. Risdiplam (Evrysdi) is being evaluated in two ongoing Phase 2/3 trials (FIREFISH, SUNFISH) and an ongoing, phase 2 trial (RAINBOWFISH). FIREFISH is evaluating patients with infantile-onset Type I SMA and SUNFISH is evaluating patients with later-onset Type II and non-ambulatory Type III. RAINBOWFISH is enrolling pre-symptomatic infants two months of age or younger with SMA. All three studies require a confirmed diagnosis of 5q-autosomal recessive SMA prior to enrollment. Patients requiring invasive ventilation or tracheostomy are excluded from all three clinical trials (FIREFISH, SUNFISH, RAINBOWFISH); therefore, there are no data to show efficacy and safety in this patient population.

IV. FIREFISH is an open-label, two-part study designed to assess safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD). The study included 21 patients in Part One and 41 patients in Part Two aged one to seven months with Type I SMA. The following endpoints were used: Bayley Scales of Infant Development–Third Edition (BSID-III) Item 22, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), and Hammersmith Infant Neurologic Exam (HINE).

- BSID-III is a clinical evaluation developed to help identify children with developmental delay who may require intervention services. The BSID-III consists of three areas of development: cognitive, language, and motor. Effectiveness was established based on the ability to sit without support for at least five seconds (as measured by Item 22). This scale is intended for pediatrics only and is not specific to SMA.
- CHOP-INTEND is a validated, 16-item, 64-point scale, designed to measure motor function for weak infants with Type I SMA and is intended for pediatrics only. It measures spontaneous upper and lower extremity movement, hand grip, head in midline with visual stimulation, hip adductors, rolling from legs and arms, shoulder and elbow flexion by itself and in addition to horizontal abduction, knee extension, hip flexion an foot dorsiflexion, head control, head/neck extension, and spinal

incurvation. Each of the 16 items is graded on a scale of zero to four, with zero meaning no response and four meaning complete response.

- HINE-2 is an SMA-specific measurement, 8-item, 26-point scale, designed to measure motor skills in infants with SMA. A score of zero for items such as sitting, crawling, and walking is expected for Type I. It measures voluntary grasp, ability to kick, head control, rolling, sitting, crawling, standing, and walking.
- The primary efficacy outcome in FIREFISH Part One was dose determination for Part Two of the study, which was 0.2 mg/kg/day. The primary efficacy outcome in FIREFISH Part Two was the proportion of infants sitting without support for at least five seconds as assessed by the Gross Motor Scale of the BSID-III at Month 12, which was 29% (90% CI: 17.8 to 43.1%). Key secondary efficacy outcomes in FIREFISH Part One include BSID-III at Month 12, which was 33%; infants alive with no permanent ventilation, 90.5%; proportion of infants who require hospitalization, and 38% did not require hospitalization. Key secondary efficacy outcomes in FIREFISH Part Two include HINE-2, which was 78% ($p<0.0001$) while the proportion of patients who achieved at least four points on the CHOP-INTEND score was 90% ($p<0.0001$).

V. SUNFISH is a two-part randomized, placebo-controlled study designed to assess safety, tolerability, efficacy, PK, and PD. The study included 51 patients in Part One and 180 patients in Part Two aged two to 25 with Type II or III SMA. Patients in Part Two of SUNFISH were randomized. The following endpoints were used: Motor Function Measure 32 (MFM-32) and Revised Upper Limb Module (RULM).

- MFM-32 is a 32-item scale that measures motor function abilities that relate to daily functions. The total MFM-32 score is expressed as a percentage (range: zero to 100) of the maximum possible score, with higher scores indicating greater motor function. This scale is suitable for assessing gross and fine motor skills in children and adult patients.
- RULM is a 19-item scorable scale used to assess motor performance of the upper limb in ambulatory and non-ambulatory patients with SMA. It tests proximal and distal motor functions of both upper limbs. The total score ranges from zero (all the items cannot be performed) to 37 (all the activities are achieved fully without any compensatory maneuvers). Each item is scored from zero to two: zero= unable, one=able with modification, two=able with no difficulty. RULM is applicable to both children and adults with SMA.
- The primary efficacy outcome in SUNFISH Part Two was the change from baseline to Month 12 in the MFM32 score in risdiplam (Evrysdi) vs. placebo, which was 1.36 (95% CI 0.61, 2.11) vs. -0.19 (-1.22, 0.84), with a difference from placebo of 1.55 (95% CI 0.30, 2.81, p=0.0156). Key secondary outcomes in SUNFISH Part Two include the proportion of patients with a 3-point or greater change from baseline to Month 12 in the MFM32 total score in risdiplam (Evrysdi) vs. placebo, which was 38.3% (28.9, 47.6) vs. 23.7% (12.0, 35.4), with a difference from placebo of 2.35 (1.01,

5.44), p-value=0.0469; change from baseline in total score of RULM at Month 12 in risdiplam (Evrysdi) vs. placebo of 1.61 (1.00, 2.22) vs. 0.02 (-0.83, 0.87), with a difference from placebo of 1.59 (0.55, 2.62), p-value=0.0469.

VI. While primary endpoint was measured at Month 12, patients showed improvement at Month 6. In FIREFISH Part Two, 38 of 41 infants surpassed responder threshold (≥4-point CHOP-INTEND improvement) at Month 6. Moreover, at Month 12, the same number of infants (38 of 41) achieved ≥4-point CHOP-INTEND improvement. SUNFISH Part Two had follow-up visits every five weeks and appeared to significantly show greater changes in MFM32 from baseline compared to placebo starting at week 16.

VII. RAINBOWFISH is an ongoing phase 2 open-label, single-arm study designed to assess efficacy and safety of risdiplam (Evrysdi) in infants less than two months of age with pre-symptomatic SMA. The primary endpoint will assess the efficacy of risdiplam (Evrysdi) in infants with two *SMN2* copies and CMAP ≥1.5 mV at baseline based on the ability to sit without support for at least 5 seconds as measured by Item 22 of the Gross Motor Scale of the BSID-III after 12 months on treatment. Secondary endpoints will evaluate all enrolled infants (regardless of *SMN2* copy number) on the development of clinical symptoms of SMA, achievement of motor milestones as defined in the BSID-III and the HINE-2, ability to swallow and feed orally, CHOP-INTEND motor function scale, growth measures, and time to permanent ventilation and/or death.

- A total of 26 patients with pre-symptomatic SMA are currently enrolled and preliminary data (data cut off July 2021) is available for 7 patients (four patients had 2 copies of the *SMN2*, two patients had 3 copies, and one patient had >4 copies) treated with risdiplam (Evrysdi) for at least 12 months. Interim efficacy data showed patients treated with risdiplam (Evrysdi) achieved motor milestones (measured by the HINE-2) within WHO windows for healthy children at 12 months. All seven patients were alive at 12 months without permanent ventilation, achieved sitting without support, were able to feed exclusively by mouth, and maintained the ability to swallow solid food. In the six patients with two or three copies of the *SMN2* genes, four patients (67%) were able to stand and 3 patients (50%) were able to walk independently at month 12. Interim safety data is consistent with the safety profile of risdiplam (Evrysdi) for pediatric and adult patients with symptomatic SMA. The most common adverse events included teething (33%), nasal congestion (28%), and pyrexia (28%). There were no reported deaths or treatment-related adverse events that led to withdrawal at data cut off. No treatment related serious adverse events were reported in patients treated for up to 22.8 months. Full efficacy and safety data RAINBOWFISH has not been published.

VIII. Baseline documentation of motor function/milestones for patients younger than 2 months of age proactively requesting risdiplam (Evrysdi) may not be available at the time of the request. To avoid delaying access to initial therapy in recently diagnosed infants, assessments completed shortly posttherapy may serve as baseline.

IX. Other acceptable motor measurements not measured in risdiplam (Evrysdi) trials, but are validated are the following: Hammersmith Functional Motor Scale Expanded (HFMSE) and Six-Minute Walk Test (6MWT)

- HFMSE is a 33-item scorable scale used to assess motor function in people with SMA Type II or Type III; this is intended for individuals older than 24 months of age. Each item is scored from zero (lowest item grade) to two (highest item grade), with a maximum score of 66. Higher scores indicate increased levels of ability. Scorable items include, but not limited to, plinth/chair sitting, long sitting, one to two hands to head in sitting, spine to side-lying, rolls prone to supine over right and left, rolls supine to prone over right and left, sitting to lying, props on forearms, lifts head from prone, prop on extended arms, lying to sitting, 4-point kneeling, crawling, and stepping.
- 6MWT is an objective evaluation of functional exercise capability in ambulatory patients with later-onset (Type II or Type III) SMA. This test is based on distance where the patient walks as far as possible in six minutes; test is performed on a linear 25-meter marked course.

X. As of June 2022, the International Conference on the Standard of Care for Spinal Muscular Atrophy guidelines have not been updated to include risdiplam (Evrysdi) for the treatment of SMA.

XI. Per the Working Group for SMA-positive infants (comprised of 15 SMA experts), a pediatrician's expertise in child healthcare may be broad and not cover the unique features of a rare neuromuscular disorder; similarly, a general child neurologist may not specialize in the role of the neuromuscular system of the patient's symptomatology and diagnosis and may not have the knowledge to administer the specific tests being recommended here. A neuromuscular specialist would have the deepest knowledge of the clinical manifestations of SMA in order to detect the earliest symptomatology, in addition to experience with administering the highly sensitive assessments of motor neuron function and SMA specific motor function.

XII. Nusinersen (Spinraza) is a chronic, intrathecally administered therapy. Use of risdiplam (Evrysdi) in patients (1-60 years of age) previously treated with nusinersen (Spinraza) or onasemnogene abeparvovec-xioi (Zolgensma) is currently being studied (JEWELFISH trial). Interim exploratory efficacy data suggest stabilization in motor function measured by change from baseline in motor function measure (MFM-32) at 12 months of treatment and the overall adverse event profile of risdiplam (Evrysdi) has been consistent with that in treatment naïve patients. At this time, there is no evidence to suggest efficacy and safety concerns of risdiplam (Evrysdi) in patients previously treated with nusinersen (Spinraza) or onasemnogene abeparvovec-xioi (Zolgensma).

XIII. Onasemnogene abeparvovec-xioi (Zolgensma) is a one-dose treatment and it is not a cure. Patients who previously received onasemnogene abeparvovec-xioi (Zolgensma) may continue to show signs and symptoms of SMA. Clinical deterioration is defined as, but not limited to, sustained decrease in CHOP-INTEND score over a period of six months (primary endpoint in the

onasemnogene abeparvovec-xioi (Zolgensma) pivotal trial), increased frequency of breathing support (e.g., BiPAP machine at night, cough assist machine), and/or requirement of feeding. tubes.

Investigational Uses

I. Risdiplam (Evrysdi) has not been FDA approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Use in members with Type IV SMA
      i. Risdiplam (Evrysdi) has not be studied in this population.
   B. Use in combination with nusinersen (Spinraza)
      i. Risdiplam (Evrysdi) has not been studied as combination use with nusinersen.

Appendix

I. There are no specific contraindications or warnings and precautions to using risdiplam (Evrysdi)
II. Table 1: risdiplam (Evrysdi) Adult and Pediatric Dosing Regimen by Age and Body Weight

Age and Body Weight	Recommended Daily Dosage
Less than 2 months of age	0.15mg/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

References

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6. Finkel RS, Mercuri E, Meyer OH 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 2018:197-207. Available from: https://www.nmd-journal.com/article/S0960-8966(17)31290-7/pdf
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Related Policies

Currently there are no related policies.

Policy Implementation/Update

Action and Summary of Changes	Date
Updated criteria to include coverage in pre-symptomatic patients with two or three copies of SMN2 gene. Removed use in pre-symptomatic patients from E/I. Updated supporting evidence and references section.	06/2022
Policy created	11/2020