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Policy Number: C20580-A

Evrysdi (risdiplam)

PRODUCTS AFFECTED

Evrysdi (risdiplam)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:

Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:

Spinal muscular atrophy (SMA)

REQUIRED MEDICAL INFORMATION:

This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. SPINAL MUSCULAR ATROPHY (SMA):

1. Documented diagnosis of spinal muscular atrophy Type I, II, or III
AND
2. Documentation confirming BOTH of the following [DOCUMENTATION REQUIRED]:

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- a. The mutation or deletion of genes in chromosome 5q resulting in one of the following:
 - i. Homozygous gene deletion or mutation (e.g., homozygous deletion of exon 7 at locus 5q13)
OR
 - ii. Compound heterozygous mutation (e.g., deletion of SMN1 exon 7 [allele1] and mutation of SMN1 [allele2])
- AND
- b. Member has at least two copies of Survival Motor Neuron 2 (SMN2) gene
- AND
3. Prescriber attests that member is NOT dependent on any of the following:
 - a. Permanent ventilation defined as tracheostomy or ≥ 16 hours of noninvasive ventilation per day or intubation for ≥ 21 consecutive days in the absence of, or following the resolution of, an acute reversible event
OR
 - b. Awake non-invasive ventilation (use of non-invasive ventilation beyond naps and nighttime sleep), or with awake hypoxemia (arterial oxygen saturation less than [$<$] 95%) with or without ventilator support
- AND
4. Documentation of member's baseline motor function assessment using at least ONE of the following assessment tools appropriate for age and motor function (See Appendix 2) [DOCUMENTATION REQUIRED]:
 - a. BSID-III: Bayley Scales of Infant and Toddler Development, Third Edition Gross Motor Scale
 - b. CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
 - c. HINE-2: Hammersmith Infant Neurologic Exam Part 2
 - d. MFM-32 or MFM-20: Motor Function Measure
 - e. HFMS (Hammersmith Functional Motor Scale)
 - f. HFMS (Hammersmith Functional Motor Scale Expanded) or Revised Hammersmith Scale (RHS)
 - g. RULM: Revised Upper Limb Module
 - h. 6MWT: 6-minute walk test
- AND
5. a. Prescriber attests or clinical reviewer has found Evrysdi is not prescribed with, or intended for concurrent use with, Spinraza (nusinersen)
OR
b. If member is currently on Spinraza, documentation of intent to discontinue therapy [DOCUMENTATION REQUIRED]
- AND
6. Prescriber attests the member has not previously received gene replacement therapy for the treatment of SMA.

CONTINUATION OF THERAPY:

A. SPINAL MUSCULAR ATROPHY (SMA):

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
AND
2. Documentation of at least ONE positive clinical response based on provider's assessment (evaluated within 30 days of request) documenting clinically meaningful improvement or maintenance of function from pre-treatment baseline status [DOCUMENTATION REQUIRED]:
 - a. BSID-III: Bayley Scales of Infant and Toddler Development, Third Edition Gross Motor Scale
 - b. CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

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- c. Hammersmith Infant Neurologic Exam Part 2 (HINE-2)
 - d. MFM-32 or MFM-20: Motor Function Measure
 - e. HFMS (Hammersmith Functional Motor Scale)
 - f. HFMS (Hammersmith Functional Motor Scale Expanded) or Revised Hammersmith Scale (RHS)
 - g. Revised Upper Limb Module (RULM) score
 - h. 6-minute walk test (6MWT)
 - i. Member remains permanently ventilator-free
- AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
- AND
4. Prescriber attest or clinical reviewer has found Evrysdi is not prescribed with Spinraza (nusinersen) and member has not received gene replacement therapy for the treatment of SMA

DURATION OF APPROVAL:

Initial authorization: 12 months; Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified pediatric neurologist or neurologist with experience in the diagnosis and management of spinal muscular atrophy (SMA) [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

No restriction

QUANTITY:

Less than 2 months of age: 0.15 mg/kg once daily

2 months to less than 2 years of age: 0.2 mg/kg once daily

2 years of age and older weighing less than < 20 kg: 0.25 mg/kg once daily

2 years of age and older weighing 20 kg or more: 5 mg once daily

Maximum Quantity Limits – 5 mg /day

PLACE OF ADMINISTRATION:

The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Oral

DRUG CLASS:

Spinal Muscular Atrophy - Survival motor neuron 2 (SMN2) splicing modifier

FDA-APPROVED USES:

Indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients

COMPENDIAL APPROVED OFF-LABELED USES:

None

APPENDIX

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APPENDIX 1: Classification of Spinal Muscular Atrophy

A classification system based on age of symptom onset and highest ever motor function achieved has been widely adopted to describe SMA types I-IV (*Wang 2007*). More recently, the updates to the standards of care have classified phenotypes by age of onset, highest level of motor function achieved or their current motor function status (Non-Sitters, Sitters, and Walkers) to provide guidelines on evaluation and rehabilitation (*Mercuri 2017, 2018*) (Kolb, 2015)

SMA Type 0 Prenatal forms of SMA

- The most severe form of SMA, symptoms can often be seen in the later stages of pregnancy. Fetal movements are less than expected and, after birth, the infant will have little ability to move and may not be able to breathe and swallow independently.
- Death occurs before the age of 6 months
- No milestones achieved
- Severe weakness, joint contractures, early respiratory failure

SMA Type 1 Acute infantile SMA; Infantile SMA, Progressive muscular atrophy of infancy; Werdnig-Hoffman

- The most common type of SMA (accounts for approximately 60% of all patients with SMA)
- Onset within 6 months of birth and symptoms progress rapidly, and most infants die before 1 year of age from respiratory failure
- Infant with SMA type I face many physical challenges, including muscle weakness and trouble breathing, coughing, and swallowing. They may need breathing assistance or a feeding tube.
- Characterized by inability to sit unsupported; these babies do not reach the developmental milestone of sitting. Affected infants are developmentally delayed; most are unable to support their head or sit unassisted
- Breathing and swallowing problems that may lead to choking or gagging
- Two copies of the SMN2 gene are usually present

SMA Type II Chronic infantile form; Childhood SMA; Chronic SMA; Dubowitz disease

- Onset within 6 to 18 months with a less severe progression
- Typically, a child can sit independently if positioned, but is unable to walk. Many patients will ultimately lose the ability to sit
- At least three SMN2 genes are usually present

SMA Type III Chronic juvenile; Juvenile SMA; Kugelberg-Welander disease;

- May be classified further as type 3a (18 months to 3 years of age) and type 3b (> 3 years old)
- Usually diagnosed after 18 months of age, but before three years of age. However, SMA type III can be diagnosed as late as the teenage years.
- Individuals affected by SMA type III are initially able to walk but have increasingly limited mobility as they grow and eventually, many need to use a wheelchair.
- Characterized by loss of ability to walk during childhood (or later during adolescence or adulthood), usually presenting as progressive proximal weakness but without respiratory muscle weakness
- Usually four to eight SMN2 genes are present

SMA Type IV Adult-onset SMA

- Rare and mildest form of SMA
- Usually surfaces in adulthood: as early as age 18 but usually presents in the third decade of life
- Leads to mild motor impairment; patients remain ambulatory but may have hip and shoulder girdle weakness mimicking a mild limb-girdle muscular dystrophy

Informational Note: The approval of Evrysdi (risdiplam) was based on data from 2 clinical studies (FIREFISH and SUNFISH) that evaluated the efficacy and safety of risdiplam in patients with Types 1, 2, and 3 SMA with infantile-onset and later-onset SMA. Therefore, insufficient evidence to support safety and efficacy of risdiplam in SMA Type 0 or 4.

APPENDIX 2: Motor Function Assessment for SMA

<p style="text-align: center;">Appropriate for Infants and Young Children with SMA <i>*Months noted reflect the age at which the various motor function scales have been validated</i></p>	
SMA Outcome Measures	Description
<p style="text-align: center;">BSID-III Gross Motor Scale of the Bayley Scales of Infant and Toddler Development Third Edition</p>	<ul style="list-style-type: none"> Individually administered to measure both cognitive and motor development and tests the behavior of infants; 1-42 months of age Assesses five domains: cognitive, language, motor, social-emotional, and adaptive skills Range of scores: 0-72
<p style="text-align: center;">CHOP-INTEND Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders</p>	<ul style="list-style-type: none"> Clinician-administered to assess motor function in infants; 1-38 months of age Validated for use in SMA Type 1 infants; specifically designed to assess extremely weak infants with SMA Type 1 Includes 16 items: each of which is scored on a 0 to 4-point scale (0 for no response, 1 for minimal, 2 for partial, 3 for nearly full, 4 for complete) Range of scores: 0-64 (higher scores indicate better function)
<p style="text-align: center;">HINE-2 Hammersmith Infant Neurological Exam Section 2</p>	<ul style="list-style-type: none"> Clinician-administered to evaluate the development of motor function; 2-24 months Measures achievement of 26 motor milestones in 8 areas (i.e., walking, standing, crawling, rolling, kicking, grasping, sitting, and head control) Range of scores: 0-26 (higher scores indicate better function)
<p style="text-align: center;">MFM-32; MFM-20 Motor Function Measure</p>	<ul style="list-style-type: none"> Measures gross and fine motor skills in children and adults Validated measure in terms of reproducibility, construct validity, and concurrent validity in patients aged between 6 and 60 years old with one of the principal neuromuscular diseases; ≥ 24 months Applicable to all degrees of disease severity, in both ambulant and non-ambulant patients MFM-32 assesses 32 different motor functions across a wide range of people with SMA assessing 3 functional areas: standing position and transfers, axial and proximal motor function, and distal motor function MFM-20 is the 20-item, short version of the MFM-32 and appropriate for follow-up of young patients or in clinical trials with a transition to the MFM-32 Range of scores: 0-100 (higher scores indicate better function), expressed as a percentage of maximum raw score
<p style="text-align: center;">HFMSE Hammersmith Functional Motor Scale-Expanded</p>	<ul style="list-style-type: none"> Clinician-administered to measure gross motor function in children and adults (later-onset SMA Type 2 and 3) including non-ambulatory and ambulatory patients); ≥ 24 months Assessment includes 33 items total; per-item scores range from 0 (unable to perform activity) to 2 (able to perform activity without assistance or modification) 3-point change is considered clinically significant Range of scores: 0-66 (higher scores indicate better function)

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<p style="text-align: center;">RHS Revised Hammersmith Scale</p>	<ul style="list-style-type: none"> • International collaboration (SMA REACH UK, Italian SMA Network and PNCRN USA) undertook an iterative process to address discontinuity in the recorded performance of the HFMSE and developed a revised functional scale using Rasch analysis • Clinician rated outcome measure to assess physical abilities in SMA type 2 through to strong ambulant SMA type 3 patients • 36-item assessment of motor/functional ability for those with non-ambulatory (type II and III) and ambulatory (type III) SMA • Construct and concurrent validity were also confirmed with a strong significant positive correlation with the WHO motor milestones
<p style="text-align: center;">RULM Revised Upper Limb Module</p>	<ul style="list-style-type: none"> • To measure upper limb function in SMA patients; proximal and distal motor functions of the arm; ≥ 30 months • Range of scores: 0-37 (0: all the items cannot be performed; 37: all the activities are achieved fully without any compensatory maneuvers)
<p style="text-align: center;">6MWT 6-Minute Walk Test</p>	<ul style="list-style-type: none"> • Exercise capacity in ambulatory patients ≥ 44 months (later-onset Type 2 or 3 SMA) • Measures the maximum distance a patient can walk in 6 minutes over a 25-meter linear course • Range of scores: measured in meters

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Spinal Muscular Atrophy (SMA)

SMA is a group of genetic disorders characterized by progressive degeneration of spinal cord and brainstem motor neurons resulting in hypotonia, atrophy of skeletal muscles, and generalized weakness.

- Caused by a defect in the survival motor neuron 1 (SMN1) gene located on chromosome 5q13, with nearly all cases resulting from deletion, rearrangement, or mutation in SMN1. Absence of SMN1 leads to reliance on the nearly identical SMN2 gene; however, SMN2 produces a small amount of SMN protein, but the amount of functional SMN protein produced is insufficient to compensate for the loss of the SMN1 gene. (AHFS 2018)
- Associated with multiple clinical problems that affect respiratory, nutritional, orthopedic, rehabilitative, emotional, and social aspects of the disease. The clinical manifestations and disease severity of SMA are highly variable (Wang, 2007).
- 4 types of SMA with type 1 being evident at birth and each of the other types typically manifesting in successively older age groups. [Refer to APPENDIX 1: Classification of Spinal Muscular Atrophy]
- Age of onset is a predictor of the person's maximal motor function, with earlier onset associated with more severe disease (Farrar et al.) Onset occurs before 6 months of age in about 60% of affected individuals; these patients usually do not live past 2 years old (Ross et al.).
- Affects 1 in 6,000 to 1 in 10,000 people (Genetics Home Reference [GHR], 2017).
- About 95%-98% of patients are homozygous for SMN1 gene defect (both parents carry recessive gene defect)
- About 2% of patients have heterozygous gene defects with a de novo SMN1 mutation
- Current standard treatment is not curative, but focuses on supportive and preventive measures that address the effects of muscle weakness and related clinical problems that develop with age (Wang, 2007)

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- Treatments should address minimizing complications and may include:
Pulmonary treatments including airway clearance and if needed, respiratory support
Improving sleep quality through nocturnal noninvasive ventilation (often with bi-level positive pressure)
Optimization of nutritional status
Maintenance of fitness and endurance through regular exercise
Occupational therapy to help with management of truncal and limb weakness

Summary of Clinical Trials

Four Phase 2 or Phase 3 trials of Evrysdi (FIREFISH, SUNFISH, JEWELFISH, and RAINBOWFISH) are evaluating the treatment's efficacy and safety in a wide range of SMA patients

FIREFISH (infantile-onset) and SUNFISH (later-onset) lead to the approval of Evrysdi and evaluated the efficacy in patients aged 2 months to 25 years who have not previously received treatment for SMA. The patient population studied in the pivotal trials (FIREFISH and SUNFISH) is similar to the population studied for Spinraza, patients who have not previously received treatment for SMA.

- FIREFISH in symptomatic infants aged 2 to 7 months; SUNFISH in children and adults aged 2 to 25 years
- SUNFISH is the first placebo-controlled trial to include adults with Types 2 and 3 SMA.

After finishing in their respective trial, SUNFISH and FIREFISH patients are offered the opportunity to enter an open-label extension study where all will receive Evrysdi.

- *Evrysdi has not been studied in patients that require permanent ventilation in any sub-type of SMA. Therefore, Evrysdi is considered investigational in patients who already require permanent ventilation due to the lack of evidence demonstrating safety and efficacy in those patients. No patients in the FIREFISH or SUNFISH trial required permanent ventilation at baseline. Ventilation and respiration are also secondary efficacy endpoints, time to permanent ventilation (as defined in above criteria), percentage of infants who are alive without permanent ventilation at Month 12 and 24, and proportion of infants not requiring respiratory support (invasive or non-invasive) at 12 and 24 months*

RAINBOWFISH: Studying pre-symptomatic SMA infants and is similar to the NURTURE trial for Spinraza.

JEWELFISH: Evaluating Evrysdi's safety and tolerability in a broad range of SMA patients, ages 6 months to 60 years, all previously treated with another SMA-targeted therapy, including Spinraza and Zolgensma.

Pivotal Trial Results

The overall findings showed clinically meaningful improvements in motor function across two clinical trials in people with varying ages (2 months of age and older) and levels of disease severity, including Types 1, 2, and 3 SMA.

Pediatric, Infantile-onset SMA

In an open-label small study of infants with type 1 SMA who received their first dose within 4 months of symptom onset, risdiplam-treated patients achieved a significant gross motor milestone response [41% (7/17)] measured using the Bayley Scales of Infant and Toddler Development (BSID-III) score. The majority infants [90% (19/21)] survived without permanent ventilation at 12 months and achieved the ability to sit without support, a key motor milestone not normally seen in the natural course of the disease.

Evrysdi also improved survival without permanent ventilation at 12 and 23 months, compared to natural history.

FIREFISH An open-label, two-part pivotal study, was designed to assess Evrysdi safety, tolerability, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) in patients aged 1 to 7 months with Type

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1 SMA. Part 1 evaluated several doses of Evrysdi and determined the therapeutic dose of 0.2 mg/kg for Part 2.

In Part 1, after 12 months of Evrysdi treatment:

- 41% (7/17) of infants treated with the therapeutic dose achieved the ability to sit without support for at least 5 seconds as measured by the BSID-III gross motor scale.
- 90% (19/21) of all infants were alive without permanent ventilation* and reached 15 months of age or older
- 81% (17/21) of all patients were alive without permanent ventilation* after a minimum of 23 months of treatment and reached an age of 28 months or older (median 32 months; range 28 to 45 months)

Pediatric, Later-onset SMA

Significantly more patients treated with 12 months of risdiplam had clinically significant improvements in Motor Function Measure 32 (MFM32) scores compared with placebo in a randomized study of patients 2 to 25 years with later-onset SMA. Younger patients and those with a shorter disease duration had a greater benefit with treatment.

SUNFISH (NCT02908685) A two-part placebo-controlled multicenter pivotal trial, was designed to assess Evrysdi safety, tolerability, efficacy, PK and PD in people with Type 2 or 3 SMA aged 2 to 25, including those with scoliosis (67% in Part 2) and joint contractures at baseline. In Part 2, after 12 months, Evrysdi treatment led to:

- A clinically meaningful and statistically significant improvement in motor function among children and adults, as measured by a change from baseline in the MFM-32 total score (1.55-point mean difference), at 12 months as compared to placebo (1.36 points; -0.19 points, respectively)
- Improved upper limb motor function compared to baseline, as measured by the RULM, a secondary independent motor function endpoint of the study (1.59-point difference)

Pivotal Trial Safety Data

The safety profile of Evrysdi was established across the FIREFISH and SUNFISH pivotal trials

- The most common adverse reactions in later-onset SMA (incidence of at least 10% of patients treated with Evrysdi and more frequently than control) were fever, diarrhea, and rash.
- The most common adverse reactions in infantile-onset SMA were similar to those observed in later-onset SMA patients. Additionally, the most common adverse reactions (incidence of at least 10%) were upper respiratory tract infection, pneumonia, constipation, and vomiting.

Infantile-Onset SMA			
NCT Number	Description	Phase	Status/NCT Number
FIREFISH	Safety, Tolerability, PK, PD and Efficacy of Evrysdi in Infants with Type1 SMA	II/III	NCT02913482 Complete Part 2 Ongoing (n=41) Actual Completion: December 2023

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A two-part, open-label, pivotal study in symptomatic infants aged 2 to 7 months with Type 1 SMA (symptom onset between 28 days and 3 months of age)

Study Population

- Infantile-onset type 1 SMA
- 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
- Median age of symptom onset: 2 months (range: 0.9 to 3.0)
- Median age at enrollment: 6.7 months (range: 3.3–6.9)
- Median time between symptom onset and first dose: 4.0 months (range: 2.0–5.8)
- 71% female; 81% Caucasian and 19% Asian

Part 1 (n = 21) provides efficacy and safety data in patients with Type 1 SMA. Patients (n = 21) were enrolled in one of two dosage cohorts. Patients in the higher-dosage cohort (n=17) had their dosage adjusted to the recommended dosage of 0.2 mg/kg/day before 12 months of treatment, while patients in the low-dosage cohort (n=4) did not. Additional safety information is provided by Part 2 (n=41) in patients with Type 1 SMA.

Part 2 (n=41) assessed efficacy as measured by the proportion of infants with 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 based on survival without permanent ventilation.

Intervention: Recommended dose found to be 0.2 mg/kg/day administered orally once daily.

Primary Endpoint	Proportion of infants sitting without support for at least 5 seconds after 12 months of treatment as measured by Gross Motor Scale of the BSID-III
Key Secondary Endpoints <i>*FIREFISH has numerous secondary outcome measures</i>	Secondary trial endpoints include the percentage of infants who experience adverse events, changes in blood biomarkers, and assessments of milestones reached in the children's development

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<p>Motor Milestone Achievement</p>	<p>Part 1 (n=21) assessed the safety profile of risdiplam by evaluating several doses of Evrysdi and determined the therapeutic dose of 0.2 mg/kg for Part 2. At 12 months of treatment, among the infants who received the dose selected for the confirmatory Part 2 of the study, (n=17):</p> <p>41% (n = 7/17) of infants treated with the therapeutic dose achieved the ability to sit without support for at least 5 seconds as measured by the BSID-III gross motor scale after 12 months of treatment. These results demonstrate a clear divergence from natural history where babies with Type 1 SMA never achieve these milestones. In the natural history of untreated infantile-onset SMA, patients would not be expected to attain the ability to sit independently, and no more than 25% of these patients would be expected to survive without permanent ventilation beyond 14 months of age.</p> <ul style="list-style-type: none"> • 64.7% (11/17) infants were able to sit (with or without support) • 53% (9/17) infants were able to maintain an upright head position (HINE-2, n=17) • 59% (10/17) infants demonstrated rolling (rolling to the side, prone to supine, or supine to prone) (HINE-2, n=17) • 6% infant (1) was able to stand (HINE-2, n=17) • <i>*Bayley Scales of Infant and Toddler Development, Third Edition Gross Motor Scale</i>
<p>Survival</p>	<ul style="list-style-type: none"> • 85.7% (18/21) babies were event-free overall • Three infants experienced fatal complications of their disease after approximately 1, 8, and 13 months of treatment. None of these has been attributed by the investigator as related to risdiplam. • A fourth infant died during safety follow up at 24 months
<p>Pulmonary Function and Swallowing</p>	<ul style="list-style-type: none"> • 90% (n=19/21) of patients were alive without permanent ventilation after 12 months of treatment and reached 15 months of age or older • 81% (n=17/21) of patients were alive without permanent ventilation after 23 or months of treatment and reached an age of 28 months or older (median 32 months; range 28-45 months) <p>No child required tracheostomy or permanent ventilation nor lost the ability to swallow</p> <p><i>*Permanent ventilation defined as tracheostomy or ≥16 hours of noninvasive ventilation per day or intubation for ≥21 consecutive days in the absence of, or following the resolution of, an acute reversible event.</i></p>
<p>CHOP-INTEND</p>	<ul style="list-style-type: none"> • 59% (11/17) achieved a score of 40 or above • Median change from baseline CHOP-INTEND score was 17.5
<p>The most common adverse events included fever (pyrexia; 52.4%), upper respiratory tract infections (42.9%), diarrhea (28.6%), vomiting (23.8%), cough (23.8%) pneumonia (19.0%) and constipation (19.0%). No significant ophthalmological findings to date (data cutoff 27 February 2019).</p> <p>No patients withdrew from the study because of safety issues, and no new safety signals were identified in the trial.</p>	

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Later-Onset SMA			
NCT Number	Description	Phase	Status/NCT Number
<u>SUNFISH</u>	Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Evrysdi in Type 2 and 3 SMA Participants	II/III	NCT02908685 Complete Part 2 (n=231) Actual Completion: October 2023

A two-part, double-blind, placebo-controlled, pivotal study in people aged 2 to 25 years (n=180) with type 2 and 3 SMA, with broad inclusion criteria (NOTE: Both type 2 and type 3 are less severe than type 1 disease)

- Part 1: Dose-finding and exploratory in 51 patients (14% ambulatory)
- Part 2: 180 non-ambulatory patients with Type 2 (71%) or Type 3 (29%) SMA (Table 1)
- All non-ambulatory, but able to sit independently; 67% had scoliosis
- Median age of symptom onset: 15.5 months
- Median age at enrollment: 9 years (range: 2–25)
- Median time between symptom onset and first treatment: 102.6 months (range, 1-275)
- 51% female; 67% Caucasian 19% were Asian
- At baseline: 67% of patients had scoliosis (32% with severe scoliosis)
- Mean baseline scores: MFM32 score: 46.1 and RULM score: 20.1
- Overall baseline demographic characteristics were reasonably balanced between the treatment groups (EVRYSDI and placebo), with the exception of scoliosis (63% in the EVRYSDI arm vs. 73% in the placebo group)

The majority of patients in the study were older, had more progressed disease as evidenced by severe scoliosis and contractures, and had lower baseline scores on motor function scales relative to other clinical trials in this patient population.

Intervention: Recommended dose found to be 0.2 mg/kg/day administered orally once daily.

Patients were randomized 2:1 to receive EVRYSDI at the recommended dosage or placebo. Randomization was stratified by age group (2 to 5, 6 to 11, 12 to 17, or 18 to 25 years of age).

Endpoint	EVRYSDI (N = 120)	Placebo (N = 60)
Primary Endpoint Change from baseline in total MFM32 score at Month 12, LS means	1.36 (0.61, 2.11)	-0.19 (-1.22, 0.84)
Difference from Placebo, Estimate	1.55 (0.30, 2.81) 0.0156	
Secondary Endpoint Proportion of patients with a change from baseline MFM32 total score of 3 or more at Month 12 (95% CI)	38.3% (28.9, 47.6)	23.7% (12.0, 35.4)

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Change from baseline in total score of RULM at Month12, LS means	1.61 (1.00, 2.22)	0.02 (-0.83, 0.87)
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Primary Endpoint	<ul style="list-style-type: none"> Change from baseline to Month 12 in the *MFM-32 score compared to placebo <p>Result: A clinically meaningful and statistically significant improvement in motor function among children and adults, as measured by a change in baseline in the MFM-32 total score (1.55 point mean difference; p = 0.0156), at 12 months as compared to placebo (1.36 points [risdiplam treatment arm -95% CI: 0.61, 2.11]; [placebo treatment arm: -0.19 points 95% CI: 1.22, 0.84])</p> <p><i>*MFM-32 is validated measure used to evaluate fine and gross motor function; assesses 32 different motor functions across a wide range of people with SMA</i></p>
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Primary Endpoint	Change from baseline to month 12 in the MFM-32 score (Part 1) Ref
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MFM32	Aged 2-11 (n=24)	Aged 12-25 (n=19)	Aged 2-25 (n=43) *
Total MFM change from baseline, mean (SD)	3.47 (3.77)	1.64 (3.43)	2.66 (3.70)
Total MFM change from baseline, median (range)	4.17 (-6.3, -9.4)	2.08 (-7.3, -6.3)	3.13 (-7.3, -9.4)
Proportion of patients who achieve improvement (i.e. a change from baseline in MFM score ≥ 3), % (n)	70.8 (17/24)	42.1 (8/19)	58.1 (25/43)

**Excludes 7 patients who performed the MFM20 assessment (only patients who performed the full MFM32 assessment are included in the analysis) and one patient who had dropped out of the study prior to the Month 12 visit.*

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<p>Key Secondary Endpoints</p> <p><i>*SUNFISH has numerous secondary outcome measures</i></p>	<ul style="list-style-type: none"> Proportion of patients with a 3-point or greater change from baseline to Month 12 in the MFM32 total score Result: Clinically meaningful improvements-- a 3-point or greater increase on the MFM32 scale-- seen in 78.1% of Evrysdi-treated children and 52.9% of those given a placebo Change from Baseline in the Total Score of the Revised Upper Limb Module (RULM) at Month 12: 1.61 with Evrysdi; 0.02 with placebo Result: Improved upper limb motor function compared to baseline, as measured by RULM, a secondary independent motor function endpoint of the study (1.59 point difference; p=0.0028) <p><i>*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).</i></p>
<p>The most common adverse events in Part 1 of the SUNFISH study were fever (pyrexia; 41%), cough (33%), vomiting (29%), upper respiratory tract infections (26%), persistent sore throat (oropharyngeal pain; 22%) and cold (nasopharyngitis; 20%). The most common serious adverse event that occurred in two of the 51 patients exposed to risdiplam was pneumonia. No significant ophthalmological findings to date.</p>	
<p>To date there have been no treatment-related safety findings leading to withdrawal from any study; data cutoff 09 January 2019.</p>	

ACTIVE TRIALS			
NCT Number	Description	Phase	Status/NCT Number
<p>JEWELFISH NCT03032172</p>	<p>A Study of Evrysdi in Adult and Pediatric Participants with SMA</p>	<p>II</p>	<p>Active, not recruiting Estimated primary completion: January 2022 Expected completion: December 2024</p>
<p>An open-label Phase 2 trial designed to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) in patients with SMA types 1, 2, and 3 who received prior SMA-directed therapies (Spinraza and Zolgensma)</p> <p>Primary goals are safety in these previously treated patients, measured by the percentage of adverse or serious side effects, evidence of new or worsening symptoms, and measures of blood markers including treatment concentrations.</p> <p>All participants (aged 6 months to 60 years) given Evrysdi once a day for 24 months, after which they may also enroll in the extension study. Recruitment for this study is complete with 174 people enrolled.</p>			

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<p>RAINBOWFISH NCT03779334</p>	<p>A Study of Evrysdi in Infants with Genetically Diagnosed and Presymptomatic SMA</p>	<p>II</p>	<p>Active, not recruiting Actual primary completion: February 2023 Expected completion: March 2027</p>
<p>An open-label, single-arm, multicenter study the safety, efficacy, pharmacokinetics, and pharmacodynamics in presymptomatic newborns and patients up to 6 weeks old, who are genetically diagnosed with SMA but without any evident symptoms (~n=25)</p> <p>The number of infants able to sit up without support after 12 months of treatment is the study's primary endpoint. Secondary endpoints include adverse events, the number of children who go on to develop clear SMA symptoms, and time to which they need permanent ventilation.</p>			

HAYES

An Emerging Technology Report addressing 'Evrysdi (risdiplam) for Spinal Muscular Atrophy' (published Aug 9, 2020) noted that there is 'insufficient published, peer-reviewed evidence to evaluate the safety and efficacy of Evrysdi for the treatment of SMA.'

The report noted that the results of clinical trials have not been published but have been presented:

- Interim results from the phase II/III FIREFISH study have been presented at conference proceedings. Investigators reported that 13 of 14 (93%) infants had ≥ 4-point improvement in CHOP-INTEND total score from baseline at 8 months (Baranello et al., 2019; Masson et al., 2019).
- Interim results from the phase II/III SUNFISH trial have been presented at conference proceedings. Investigators reported a sustained, > 2-fold increase in median SMN protein versus baseline following 1 year of treatment with Evrysdi (Baranello et al., 2018; Campbell et al., 2019; Pera et al., 2019).
- Interim results from the phase II JEWELFISH trial have been presented at conference proceedings. Investigators reported an up to 4 times SMN protein increase compared with baseline after 4 weeks of treatment with Evrysdi (Chiriboga et al., 2018; Chiriboga et al., 2019).

PEER-REVIEWED STUDIES

No published, peer-reviewed studies evaluating Evrysdi for the treatment of SMA were identified.

SYSTEMATIC REVIEWS/META-ANALYSES

No systematic reviews or meta-analyses regarding Evrysdi (risdiplam) treatment of SMA were identified.

CLINICAL PRACTICE GUIDELINES

No clinical practice guidelines addressing Evrysdi (risdiplam) for the treatment of SMA have been identified at this time.

National Institute for Health and Care Excellence (NICE)

Risdiplam for treating spinal muscular atrophy. Technology appraisal guidance published 16 December 2021.

Recommendations: Risdiplam is recommended as an option for treating 5q spinal muscular atrophy (SMA) in people 2 months and older with a clinical diagnosis of SMA types 1, 2 or 3.

SMA is a rare genetic condition and there is an unmet need for effective treatments that can slow disease progression. The cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources. So risdiplam cannot be recommended for routine use in the NHS. But because of

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the unmet need for effective treatments for SMA, risdiplam is recommended through a managed access agreement while more data is collected to address the uncertainties in the evidence. After consultation, the company presented 24-month follow-up data from SUNFISH and FIREFISH but noted that these studies were ongoing. The ERG noted that the 24-month data for SUNFISH was not comparative because the placebo-controlled period ended after 12 months of treatment. The clinical experts explained that there was considerable uncertainty about the long-term benefits of risdiplam but in their clinical experience the results were promising. The committee concluded that risdiplam would likely provide long-term benefits, but these are uncertain because the size and nature of the benefits are not known.

Consensus Statement for Standard of Care in Spinal Muscular Atrophy (2007)

In 2007, an International Conference on the Standard of Care for SMA published a consensus statement on SMA standard of care that has been widely used throughout the world. (Wang et al, 2007)

Diagnosis and Management of SMA

Updated Standards of Care (SOC) in SMA (Mercuri et al, 2018), expands on the topics covered in the 2007 SOC recommendations and includes information on the most updated, best practices in care for SMA. Part 1 focuses on the methods used to achieve SOC recommendations, and an update on diagnosis, rehabilitation, orthopedic and spinal management. It also covers nutritional, swallowing and gastrointestinal management.

The SMA Care Group released a two-part update in 2018 to a consensus statement from the International Conference on the Standard of Care for SMA (Wang et al., 2007). The recommendations predominantly address palliative care in managing the pulmonary, motor, and immune symptoms of SMA (Finkel et al., 2018; Mercuri et al., 2018).

Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care (2018) Guideline
Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics (2018) Guideline

Updated Standards of Care (SOC) in SMA (Finkel et al 2018), expands on the topics covered in the previous recommendations and includes information on the most updated, best practices in care for SMA. Part 2 focuses on pulmonary management, acute care, other organ involvement, ethical issues, medications, and the impact of new treatments for SMA.

Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group

Work Group comprised of clinicians and geneticists with expertise in SMA developed a treatment algorithm in 2018 for infants who have positive results from a newborn screening test (Glascock et al. 2018)

- SMA Types 1 and 2 comprise a large majority of SMA cases and account for the majority of patients who screen positively for SMA and have three or fewer SMN2 gene copies. The Working Group unanimously recommends immediate treatment for these patients to achieve a maximal response to treatment. The NURTURE trial with Spinraza that involved pre-symptomatic infants who had either two or three SMN2 gene copies supports this recommendation.
- Treatment recommendations for patients who screen positive for SMA and have only one SMN2 gene copy or four or more SMN2 gene copies is more complicated. It is likely that patients with only one SMN2 gene copy will likely be symptomatic at birth and the physician should determine if treatment is warranted.

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The Committee reached consensus that patients with more than four SMN2 copies should not be treated immediately but screened carefully for symptom presentation. (Glascock, 2018)

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Evrysdi (risdiplam) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Evrysdi (risdiplam) include: No labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:

Concurrent treatment with Spinraza (nusinersen) or Zolgensma (onasemnogene abeparvovec): JEWELFISH is evaluating Evrysdi's *safety and tolerability* in a broad range of SMA patients, ages 6 months to 60 years, all previously treated with another SMA-targeted therapy (44% previously received Spinraza; 8% previously received Zolgensma). Expected completion: December 2024. In October 2022, 2 year data was released from the JEWELFISH study. The adverse event profile observed in the JEWELFISH trial was consistent with previous Evrysdi data. The rates of adverse events decreased over each evaluation period. The JEWELFISH data demonstrate that use of Evrysdi in this population is safe. *Efficacy was not formally evaluated*, but data showed that patients receiving Evrysdi sustained their motor function and treatment with Evrysdi led to increased levels of survival motor neuron (SMN) protein.

No data have been published evaluating the efficacy of concurrent treatment with patients with SMA types 1, 2, and 3 who received prior SMA-directed therapies (Spinraza and Zolgensma).

The pharmacokinetics and safety in patients with severe hepatic impairment (Child-Pugh class C) have not been studied.

Pregnancy testing is recommended for females of reproductive potential prior to initiating Evrysdi. Advise female patients of reproductive potential to use effective contraception during treatment with Evrysdi and for at least 1 month after her last dose. Male fertility may be compromised by treatment with Evrysdi. Counsel male patients of reproductive potential receiving Evrysdi about the potential effects on fertility. Male patients may consider sperm preservation prior to treatment.

Based on in vitro data, Evrysdi may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K, such as *metformin*. Avoid administration of Evrysdi with MATE (multidrug and toxin extrusion) substrates. If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction of the coadministered drug if needed.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
N/A	

AVAILABLE DOSAGE FORMS:

Evrysdi SOLR 0.75MG/ML

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION – Notable revisions: Continuation of therapy	Q2 2024
REVISION – Notable revisions: Required Medical Information Continuation of Therapy Age Restrictions Quantity Drug Class Appendix Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms Reference	Q2 2023
REVISION – Notable revisions: FDA Approved Uses Quantity References	Q3 2022
REVISION- Notable revisions: Duration of Approval	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file