Clinical Policy: Risdiplam (Evrysdi)

Reference Number: ERX.SPA.387
Effective Date: 08.07.20
Last Review Date: 08.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Risdiplam (Evrysdi®) is a survival motor neuron 2 (SMN2) gene pre-mRNA splicing modifier.

FDA Approved Indication(s)
Evrysdi is indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

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

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Evrysdi is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Spinal Muscular Atrophy (must meet all)**:**

1. Diagnosis of SMA;
2. Genetic testing confirms the presence of one of the following (a, b, or c):
   a. Homozygous deletions of SMN1 gene (e.g., absence of the SMN1 gene);
   b. Homozygous mutation in the SMN1 gene (e.g., biallelic mutations of exon 7);
   c. Compound heterozygous mutation in the SMN1 gene (e.g., deletion of SMN1 exon 7 (allele 1) and mutation of SMN1 (allele 2));
3. Prescribed by or in consultation with a neurologist;
4. Age ≥ 2 months;
5. Documentation of genetic testing quantifying number of copies of SMN2 gene and one of the following (a or b):
   a. One, two, or three copies of SMN2 gene;
   b. Four copies of SMN2 gene, and documentation indicates presence of SMA symptoms (e.g., weakness, tremors, loss of functionality);
6. Documentation of one of the following baseline scores (*see Appendix D*) (a or b):
   a. For age < 2 years: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder (CHOP-INTEND) score or Hammersmith Infant Neurological Examination (HINE) Section 2 motor milestone score;
   b. For age ≥ 2 years: Hammersmith functional motor scale expanded (HFMSE) score, Revised Hammersmith Scale (RHS), Upper Limb Module (ULM), Revised Upper Limb Module (RULM), or 6-Minute Walk Test (6MWT);
7. Member does not require tracheostomy or invasive ventilation;
8. Evrysdi is not prescribed concurrently with Spinraza® and/or Zolgensma®;
9. If the member is currently on Spinraza, documentation of prescriber attestation of Spinraza discontinuation;
10. If the member has a history of treatment with Zolgensma, must meet both of the following (a and b):

a. Provider must submit evidence of poor response to Zolgensma (e.g., sustained decrease in CHOP-INTEND score over a period of 6 months);
b. Documentation of prescriber attestation of clinical deterioration;

11. Request meets one of the following (a, b, or c):
    a. If 2 months of age to less than 2 years of age, dose does not exceed 0.2 mg/kg per day;
    b. If 2 years of age and older, weighing less than 20 kg, dose does not exceed 0.25 mg/kg per day;
    c. If 2 years of age and older, weighing 20 kg or more, dose does not exceed 5 mg per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Spinal Muscular Atrophy (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member does not require tracheostomy or invasive ventilation;
3. Member is responding positively to therapy as evidenced by one of the following (a, b, or c):
    a. For age < 2 years, must meet one of the following (i or ii):
        i. For CHOP-INTEND, must demonstrate score improvement or maintenance of previous score improvement of ≥ 4 points from baseline;
        ii. For HINE motor milestone score, must demonstrate score improvement or maintenance of previous improvement in one or more categories AND improvement in more motor milestone categories than worsening;
    b. For age ≥ 2 years, must meet one of the following (i, ii, or iii):
        i. If first renewal since turning 2 years old, must provide submission of baseline HFMSE score, RHS score, RULM or ULM score, or 6MWT distance AND meet one of the following (1 or 2):
            1) For CHOP-INTEND, must demonstrate score improvement or maintenance of previous score improvement of ≥ 4 points from baseline;
            2) For HINE motor milestone score, must demonstrate score improvement or maintenance of previous improvement in one or more categories AND improvement in more motor milestone categories than worsening;
        ii. If ≤ 2 years at therapy initiation and request is for subsequent renewal since turning 2, must meet one of the following (*see Appendix D*) (1 or 2):
            1) For HFMSE, RHS, ULM or RULM, must demonstrate score improvement or maintenance of previous score improvement from baseline score submitted at first renewal since turning 2 years old;
            2) For 6MWT distance, must demonstrate improvement or maintenance of baseline distance;
        iii. If > 2 years at therapy initiation, must meet one of the following (1, 2, 3, or 4) (*see Appendix D*):
            1) For HFMSE or RHS, must demonstrate score improvement or maintenance of previous score improvement of ≥ 3 points from baseline;
            2) For ULM, must demonstrate score improvement or maintenance of previous improvements in ≥ 2 points from baseline;
            3) For RULM, must demonstrate score improvement or maintenance of previous improvements in ≥ 4 points from baseline;
            4) For 6MWT distance, must demonstrate improvement or maintenance of baseline distance;
    c. Member has not had a decline in motor function test score(s) from baseline AND medical justification demonstrates and supports that member is responding positively to therapy;
4. Evrysdi is not prescribed concurrently with Spinraza and/or Zolgensma;

5. If request is for a dose increase, request meets one of the following (a, b, or c):
   a. If 2 months of age to less than 2 years of age, new dose does not exceed 0.2 mg/kg per day;
   b. If 2 years of age and older, weighing less than 20 kg, new dose does not exceed 0.25 mg/kg per day;
   c. If 2 years of age and older, weighing 20 kg or more, new dose does not exceed 5 mg per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder
FDA: Food and Drug Administration
HFMSE: Hammersmith Functional Motor Scale Expanded
HINE: Hammersmith Infant Neurological Examination
MPLA: multiplex ligation-dependent probe amplification
RHS: Revised Hammersmith Scale
RULM: Revised Upper Limb Module
SMA: spinal muscular atrophy
SMN: survival motor neuron
ULM: Upper Limb Module
6MWT: 6-Minute Walk Test

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- SMA is an autosomal recessive genetic disorder. It is caused by mutations in the SMN1 (survival motor neuron) gene that is found on chromosome 5 (hence the name 5q-SMA). To develop SMA, an individual must inherit two faulty (deletion or mutation) SMN1 genes, one from each parent.
- SMN-related SMA is classified as type 1 through 4 depending on time of onset. The age of disease onset of symptoms correlates with disease severity: the earlier the age of onset, the greater the impact on motor function. Children who display symptoms at birth or in infancy typically have the lowest level of functioning (type 1). SMA onset in children (types 2 and 3), teens or adults (type 4) generally correlates with increasingly higher levels of motor function.
- SMN2 gene copy and SMA types
  - SMN2 gene copy numbers are variable in individuals with spinal muscular atrophy. Higher numbers typically correlate with less severe disease.
  - More than 95% of individuals with spinal muscular atrophy retain at least 1 copy of the SMN2 gene
  - About 80% of individuals with Type I spinal muscular atrophy have 1 or 2 copies of the SMN2 gene

- About 82% of individuals with Type II spinal muscular atrophy have 3 copies of the SMN2 gene
- About 96% of individuals with Type III spinal muscular atrophy have 3 or 4 copies of the SMN2 gene

- The CHOP-INTEND score is a validated 16-item, 64-point scale shown to be reliable and sensitive to change over time for SMA Type 1. In a prospective cohort study of SMA type I patients (n = 34), the mean rate of decline in the CHOP-INTEND score was 1.27 points/year (95% CI 0.21-2.33, p = 0.02). A CHOP-INTEND score greater than 40 is considered a clinically meaningful change.
- The HINE Section 2 motor milestone exam is an easily performed and relatively brief standardized clinical neurological examination that is optimal for infants aged between 2 and 24 months with good inter-observer reliability. This endpoint evaluates seven different areas of motor milestone development, with a maximum score between 2-4 points for each, depending on the milestone, and a total maximum score of 26 points.
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- The HFSME score combines the Hammersmith Functional Motor Scale with a 13-item expansion module for ability to distinguish motor skills among individuals who may be older or with SMA types II and III. Each item is graded from 0 to 3, with 0 signifying no response, with a total of 66 points. HFMSE has demonstrated reliability and validity in patients with SMA. An increase of greater than 2 points in total score is unlikely in untreated SMA.
- The RHS is an ordinal scale which consist of 33 items with grades of 0, 1, and 2. For individuals who can achieve the task without any compensation it is given a score of 2. For those who only attempt the movement or finish it with some form of compensation is scored 1 and sore of 0 is given when patients are unable to perform any part of the item. The total maximum score is 69 points.
- The RULM is a set of 19 tasks that measure motor function in non-ambulatory SMA patients. Each task is assessed with a 3 point ordinal scale, with a total maximum score of 37 points. Meanwhile, the maximum score for ULM was 18.
- The 6MWT is a clinical outcome measure for ambulatory SMA that has been determined to be functionally meaningful and capable of capturing disease severity.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
SMA	Weight-based dose PO QD: • 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, weigh 20 kg or more: 5 mg	5 mg/day

VI. Product Availability

For oral solution: 60 mg risdiplam as a powder for constitution to provide 0.75 mg/mL solution

VII. References

1. Evrysdi Prescribing Information. South San Francisco, CA: Genentech Inc.; April 2021. Available at: https://www.evrysdi.com/. Accessed July 20, 2021.
2. Baranello G, Servais L, Day JW, et al. FIREFISH Part 1: 1-Year results on motor function in infants with Type 1 SMA receiving risdiplam (RG7916). Presented at the Annual Meeting of the American Academy of Neurology in Philadelphia, PA; May 4–10, 2019. AAN Oral Presentation.
3. Mercuri E, Baranello G, Kirschner J, et al. Update from SUNFISH Part 1: Safety, tolerability and PK/PD from the dose-finding study, including exploratory efficacy data in patients with Type 2 or 3

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4. Wang CH, Finkel RS, Bertini ES, et al. Consensus Statement for Standard of Care in Spinal Muscular Atrophy. *Journal of Child Neurology.* 2007; 22:1027-1049.
5. Cobben JM, de Visser M, Scheffer H, et al. Confirmation of clinical diagnosis in requests for prenatal prediction of SMA type I. *J Neurol Neurosurg Psychiatry.* 1993; 56: 319-21.
6. Maitre NL, Chorna O, Romeo DM, and Guzzetta A. Implementation of the Hammersmith Infant Neurological Examination in a High-Risk Infant Follow-Up Program. *Pediatric Neurology.* 2016; 65:31-38.
7. Dunaway Young S, Montes J, Kramer SS, et al. Six-minute walk test is reliable and valid in spinal muscular atrophy. *Muscle and Nerve.* 2016. 54: 836-842.
8. Ramsey D, Scoto M, Mayhew A, et al. Revised Hammersmith Scale for Spinal Muscular Atrophy: A SMA Specific Clinical Outcome Assessment Tool. *PLoS ONE*. 2017; 12(2): e0172346. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0172346
9. Darras BT, Royden Jones H Jr, Ryan MM, et al. Neuromuscular Disorders of Infancy, Childhood, and Adolescence: A Clinician's Approach. 2nd ed. London, UK: Elsevier; 2015.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	03.10.20	05.20
Removed requirements for genetic tests within the last year and repeat testing. Amended language to require quantification of SMN2 copy number. Amended re-authorization criteria to allow for medical justification.	07.07.20	08.20
RT1: Drug is now FDA approved - criteria updated per FDA labeling: removed diagnosis language for specific type of SMA but added requirement that member is symptomatic; added age requirement; removed requirement that member does not have ophthalmological disease; removed BSID-III as an acceptable measure of response; added requirement for clinical deterioration if previously treated with Zolgensma; references reviewed and updated.	08.18.20	11.20
2Q 2021 annual review: no significant changes; references reviewed and updated.	02.12.21	05.21
Removed requirement for symptoms for members with SMN2 copies of 1 to 3.	07.20.21	08.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.