Clinical Policy: Risdiplam (Evrysdi)

Reference Number: CP.PHAR.477
Effective Date: 08.07.20
Last Review Date: 02.22
Line of Business: Commercial, HIM, 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 pediatric and adult patients.

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.

It is the policy of health plans affiliated with Centene Corporation® 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. 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);
5. 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);
6. Member does not require tracheostomy or invasive ventilation;
7. Evrysdi is not prescribed concurrently with Spinraza® and/or Zolgensma®;

8. If the member is currently on Spinraza, documentation of prescriber attestation of Spinraza discontinuation upon initiation of Evrysdi;
9. 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;
10. Request meets one of the following (a, b, c, or d):
    a. If less than 2 months of age, dose does not exceed 0.15 mg/kg per day;
    b. If 2 months of age to less than 2 years of age, dose does not exceed 0.2 mg/kg per day;
    c. If 2 years of age and older, weighing less than 20 kg, dose does not exceed 0.25 mg/kg per day;
    d. 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 (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
    a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
    b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Currently receiving medication for SMA with 1 to 4 copies of the SMN2 gene, 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, c, or d):
   a. If less than 2 months of age, new dose does not exceed 0.15 mg/kg per day;
   b. If 2 months of age to less than 2 years of age, new dose does not exceed 0.2 mg/kg per day;
   c. If 2 years of age and older, weighing less than 20 kg, new dose does not exceed 0.25 mg/kg per day;
   d. 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, 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.
- 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: • 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, 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.; May 2022. Available at: https://www.gene.com/download/pdf/evrysdi_prescribing.pdf. Accessed June 8, 2022.
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 spinal muscular atrophy (SMA) treated with risdiplam (RG7916). Presented at the Annual Meeting of the American Academy of Neurology in Philadelphia, PA; May 4–10, 2019. AAN Oral Presentation.
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.
10. ClinicalTrials.gov. A Study of Risdiplam in Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy (Rainbowfish). Available at: https://clinicaltrials.gov/ct2/show/NCT03779334. Accessed June 8, 2022.
11. Evrysdi Use in Pre-symptomatic Patients with Spinal Muscular Atrophy. Genentech Medical Information Communication; June 21, 2022.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	03.10.20	05.20
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; 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.	08.18.20	08.20
2Q 2021 annual review: no significant changes; updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); references reviewed and updated.	02.12.21	05.20
Removed requirement for symptoms for members with SMN2 copies of 1 to 3.	07.20.21	08.21
1Q 2022 annual review: revised continued therapy language to allow members to receive the medication for the appropriate indication if they had initiated the treatment outside of Centene benefit; references reviewed and updated.	09.21.21	02.22
RT4: updated criteria with new pediatric expansion indication for pre-symptomatic infants < 2 months old.	06.15.22	
Template changes applied to other diagnoses/indications.	09.28.22	

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.