BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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EVRYSDI™ (risdiplam) oral

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy 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 BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

EVRYSDI™ (risdiplam) oral

Criteria:

- **Criteria for initial therapy:** Evrysdi (risdiplam) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist or Pediatric Neurologist

2. Individual is at least 2 months of age or older up to 25 years of age

3. A confirmed diagnosis of symptomatic spinal muscular atrophy (SMA) **ONE** of the following SMA types:
    a. Infantile onset Type 1 SMA, with onset of symptoms after 28-days but prior to 3 months of age
    b. Type 2 SMA
    c. Type 3 SMA

4. Genetic testing demonstrating bi-allelic mutations or deletions in chromosome 5q in the survival motor neuron 1 (*SMN1*) gene is **ONE** of the following:
    a. Deletion of both copies of the *SMN1* gene (exon 7 at locus 5q13)
    b. Compound heterozygous of the *SMN1* gene (exon 7 at locus 5q13) is **ONE** of the following:
        i. Pathogenic variant(s) in both copies of the *SMN1* gene
        ii. Pathogenic variant in one copy and deletion of the second copy of the *SMN1* gene

5. **ONE** of the following:
    a. Patient is symptomatic and genetic test confirms 2, 3 or 4 copies of the *SMN2* gene
    b. Patient is asymptomatic and genetic test confirms minimum of 2 but less than 4 copies of the *SMN2* gene

6. Does not have the c.859G >C in exon 7 of *SMN2* gene (which predicts a milder phenotype)

7. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate
    a. Negative pregnancy test in a woman of childbearing potential
    b. Motor function and milestone assessed via an age appropriate validated exam scale (e.g., Bayley Scales of Infant and Toddler Development Third Edition (BSID-III), Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Hammersmith Functional Motor Scale Expanded (HFSME), Hammersmith Infant Neurologic Exam (HINE-2), Revised Upper Limb Module (RULM), 6-Minute Walk Test (6MWT))

8. There is **NONE** of the following:
    a. Advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence)
    b. Use of invasive ventilatory support (tracheotomy with positive pressure) or use of non-invasive ventilator support (BiPAP) for > 16 hours per day continuously for ≥ 14 days
    c. Enteral feeding
    d. Severe contractures
    e. Severe scoliosis

f. Concomitant or previous administration of virus vector-based gene therapy, e.g. Zolgensma (onasemnogene abeparvovec-xioi)
g. Concomitant or previous administration of SMN2-targeting antisense oligonucleotide, e.g. Spinraza (nusinersin)
h. Concomitant or previous administration of another SMN2 splicing modifier
i. Severe hepatic impairment (Child-Pugh Class C)
j. The patient is not concurrently enrolled in a clinical trial for any experimental therapy for SMA
k. Use after administration of Zolgensma (onasemnogene abeparvovec-xioi)
l. SMA without chromosome 5q mutations or deletions
m. Individuals having > 4 *SMN2* gene copies
n. SMA Type 0 or 4

9. There are no significant interacting drugs

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Evrysdi (risdiplam) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist or Pediatric Neurologist

2. Individual's condition responded while on therapy
    a. Response is defined as **TWO** of the following:
        i. Documentation of efficacy and disease stability by use of age appropriate evaluation tool such as CHOP-INTEND, Bayley-III Scale (motor part), HFMSE, RULM, 6-MWT, etc. of **TWO** of the following:
            1. Must demonstrate improvement or maintenance of previous scores from baseline
            2. Must demonstrate improvement in at least one more motor milestone category over baseline rather than worsening
            3. Must demonstrate improvement in more motor milestone categories than worsening over baseline
            4. Must demonstrate achieved additional motor milestone(s) over baseline
            5. No evidence of disease progression defined as a decline in motor function test score(s)
        ii. Documented evidence to support clinically meaningful stabilization or improvement in motor milestones over baseline using an age appropriate validated exam scale during previous treatment period
        iii. Reduced need for respiratory support
        iv. Prevention of permanent assisted ventilation

3. Individual has been adherent with the medication

4. There is **NONE** of the following:
    a. Advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence)

b. Use of invasive ventilatory support (tracheotomy with positive pressure) or use of non-invasive ventilator support (BiPAP) for > 16 hours per day continuously for ≥ 14 days
c. Enteral feeding
d. Severe contractures
e. Sever scoliosis
f. Concomitant or previous administration of virus vector-based gene therapy, e.g. Zolgensma (onasemnogene abeparvovec-xioi)
g. Concomitant or previous administration of SMN2-targeting antisense oligonucleotide, e.g. Spinraza (nusinersin)
h. Concomitant or previous administration of another SMN2 splicing modifier
i. Severe hepatic impairment (Child-Pugh Class C)
j. The patient is not concurrently enrolled in a clinical trial for any experimental therapy for SMA
k. Use after administration of Zolgensma (onasemnogene abeparvovec-xioi)
l. SMA without chromosome 5q mutations or deletions
m. Individuals having > 4 *SMN2* gene copies
n. SMA Type 0 or 4

5. Individual has not developed any significant adverse drug effects that may exclude continued use

6. There are no significant interacting drugs

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of a Non-cancer Medications**

2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Description:

Evrysdi (risdiplam) is a survival motor neuron 2 (SMN2) directed RNA splicing modifier indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

Risdiplam is a survival motor neuron 2 (SMN2) splicing modifier designed to treat patients with SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Using animal models of SMA, risdiplam was shown to increase exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein in the brain. *In vitro* and *in vivo* data indicate that risdiplam may cause alternative splicing of additional genes, including FOXM1 and MADD. FOXM1 and MADD are thought to be involved in cell cycle regulation and apoptosis, respectively, and have been identified as possible contributors to adverse effects seen in animals.

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In clinical trials, Evrysdi led to an increase in SMN protein with a greater than 2-fold median change from baseline within 4 weeks of treatment initiation. The increase was sustained throughout the treatment period (of at least 12 months) across all SMA types.

The safety and effectiveness of Evrysdi in pediatric patients 2 months of age and older have been established. Safety and effectiveness in pediatric patients below the age of 2 months have not been established.

SMA encompasses a spectrum of phenotypes ranging from severe forms with early onset to milder forms with later onset. The natural history of SMA according to phenotype is summarized as follows: SMA type 0 (prenatal onset) is associated with early death from respiratory failure, usually within weeks after birth; SMA type 1 (onset between birth and age six months) leads to death from respiratory failure before the age of two years; SMA type 2 (onset between 3 and 15 months of age) is notable for inability to achieve independent walking or standing but is compatible with survival into adulthood, most individuals live to age 25 years; SMA type 3 (onset between age 18 months and adulthood) is characterized by slowly progressive proximal weakness, which may lead to loss of independent ambulation, but is associated with a normal lifespan; SMA type 4 (adult onset) is otherwise similar to SMA type 3 and is associated with a normal lifespan.

Definitions:

Clinical features spinal muscular atrophy (SMA):
The diagnosis of SMA should be suspected for any infant with unexplained weakness or hypotonia. Additional suspicions suggesting the diagnosis in infants, children, or adults include a history of motor difficulties, loss of motor skills, proximal muscle weakness, hyporeflexia or areflexia, tongue fasciculations, and signs of lower motor neuron disease on examination.

All forms of SMA have diffuse symmetric proximal muscle weakness that is greater in the lower than upper limbs, and absent or markedly decreased deep tendon reflexes. In addition, SMA is associated with a restrictive, progressive respiratory insufficiency, particularly SMA type 0 and type 1.

Clinical classification spinal muscular atrophy (SMA):

Type	Age of Onset	Requires respiratory support at birth	Able to sit	Able to stand	Able to walk	Life expectancy	Predicted *SMN2* copy number
0	Prenatal	Yes	No	No	No	< 6 months	1
1	< 6 months	No	No	No	No	< 2 years	2
2	6-18 months	No	Yes	No	No	10-40 years	3
3	> 18 months	No	Yes	Yes	Assisted	Adult	3 or 4
4	> 5 years	No	Yes	Yes	Yes	Adult	> 4
Butchbach ME. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci 2016; 3:7.							

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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)]

SMA evaluation tools:

CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders)

- Measures motor function via 16 different items, which capture neck, trunk, proximal, and distal limb strength
- Scored from 0 (least function) to 4 (most function) for each of the 16 items
- Validated as part of a multicenter natural-history study and was found to reflect measures of disease severity such as number of *SMN2* copies and respiratory support needed
- A validated 64-point scale shown to be reliable and sensitive to change over time for SMA Type 1
- Maintenance scores of > 40 points is considered to be clinically meaningful in SMA

HINE (Hammersmith Infant Neurological Examination)

- Measures functional ability and achievement of motor milestones
- Consists of three sections:
    - Neurological exam (postures, cranial nerve function, reflexes, tone, and movements)
    - Development of motor function (head control, sitting, voluntary grasping, rolling, crawling, and walking)
    - State of behavior (consciousness, social orientation, and emotional state)
- The overall score ranges from 0 to 78
- At 9 or 12 months, the scores ≥ 73 are regarded as optimal
- Healthy-term infants should have a median score ≥ 67 at 3 months and ≥ 70 at 6 months

HFMSE (Hammersmith Functional Motor Scale Expanded)

- Expanded version of the original 20-item Hammersmith Functional Motor Scale that incorporates 13 items from the Gross Motor Function Measure assessment
- Consists of 33 items investigating the child's ability to perform various activities
    - Each activity (item) is scored on a 3-point system, with a score of 2 for "performs without modification," 1 for "performs with modification/adaptation," and 0 for "unable to perform."
- The total score can range from 0 (if all the activities failed) to 66 (if all the activities are achieved)
- A clinically meaningful change was estimated to be a 3-point change in the modified HFMS at 6 months in a multicenter phase 2 trial of L-carnitine and valproic acid in patients with SMA Type II or III

6MWT (6-Minute Walking Test)

- An objective evaluation of functional exercise capacity that measures the maximum distance a person can walk in 6 minutes over a 25-meter linear course
- Detects physiological fatigue in ambulatory patients with SMA as demonstrated by a 17% decrease in gait velocity from the first minute to the last
- Has been used in assessment of function and has been accepted by regulatory agencies as a clinically meaningful endpoint in other neurologic disorders

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- Has been found to be reliable in other pediatric disorders and in healthy children. Demonstrates good test-retest reliability and is sensitive to change

Revised Hammersmith scale (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

Revised upper limb module (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

Resources:

Evrysdi (risdiplam) product information, revised by manufacturer Genentec, Inc. 04-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 21, 2021.

Bodamer OA. Spinal muscular atrophy. In: UpToDate, Nordli DR, Firth HV, Martin R, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 21, 2021.

5.01.28 BCBS Association Medical Policy Reference Manual. Treatment of Spinal Muscular Atrophy. Re-view date June 2021. Accessed September 21, 2021.