Initial Approval Date: July 10, 2019
Revised Dates: January 20, 2021
September 10, 2020

CRITERIA FOR PRIOR AUTHORIZATION

Spinal Muscular Atrophy (SMA) Agents

BILLING CODE TYPE For drug coverage and provider type information, see the KMAP Reference Codes webpage.

MANUAL GUIDELINES Prior authorization will be required for all current and future dose forms available. All medication specific criteria, including drug specific indications, age, and dose for each agent is defined in Table 1 below.

Nusinersen (Spinraza®)
Onasemnogene (Zolgensma®)
Risdiplam (Evrysdi™)

CRITERIA FOR INITIAL APPROVAL FOR SMA AGENTS (Must meet the following criteria):

- Must be approved for the indication, age, and not exceed dosing limits listed in Table 1.
- Must be prescribed by or in consultation with a neurologist with expertise in the diagnosis of SMA.[3]
- Patient must have a diagnosis of spinal muscular atrophy (SMA), confirmed by SMN1 (chromosome 5q) gene mutation or deletion.[1,2,4] Must meet one of the following:
  - Homozygous SMN1 gene deletion or mutation (e.g., homozygous deletion of exon 7 at locus 5q13)[4,9]
  - Compound heterozygous SMN1 mutation (e.g., deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 [allele 2])[9]
- Prescriber must submit baseline documentation of one of the following:[6,8-10]
  - Hammersmith Infant Neurological Exam (HINE) (infant to early childhood)
  - Hammersmith Functional Motor Scale Expanded (HFMSE)
  - Upper Limb Module (ULM) Test (Non-ambulatory) or revised Upper Limb Module (RULM) Test (Non-ambulatory)
  - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)
  - Current status on motor milestones: ability to sit or ambulate.
  - Motor Function Measure 32 (MFM32).
- Patient must not be on concurrent combination therapy with more than one of the following: Evrysdi (risdiplam), Spinraza (nusinersen) or Zolgensma (onasemnogene).[5]
- Patient is not on permanent ventilation (≥ 16 hours/day for > 21 days in the absence of an acute reversible event or tracheostomy).[8-10]
- If the request is for Evrysdi (risdiplam) or Spinraza (nusinersen): Provider must submit documentation the patient has a sufficient number of copies of SMN2 gene defined as ≥ 2 copies of SMN2 gene.[1,2]
- If the request is for Evrysdi (risdiplam):
  - Patient must have symptoms of SMA.[11]
  - Patient must not have previously received Zolgensma (onasemnogene).[5]
  - Patient must meet ONE of the following:
    - Must not initiate on oral albuterol therapy during the initial approval.[6]
    - Must be stable and compliant on oral albuterol therapy for at least 6 months.[6,7]
- If the request is for Spinraza (nusinersen):
  - Must be administered by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.[8]
  - Patient must not have previously received Zolgensma (onasemnogene).[5]

APPROVED PA Criteria

- If the request is for Zolgensma (onasemnogene):
    - Patient must have bi-allelic mutations in the SMN1 gene.
    - Patient must have genetic testing that confirms the absence of c.859G>C modification on exon 7.
    - Patient must be < 2 years of age. For patients born prematurely, the corresponding full gestational age must be reached prior to administration.[9]
    - If replacing Evrysdi (risdiplam) or Spinraza (nusinersen), Zolgensma (onasemnogene) will not be prescribed concurrently as dual therapy.[5]
    - Patient must not have previously received Zolgensma (onasemnogene).[9]
    - Patient must have baseline laboratory tests demonstrating anti-AAV9 antibody titers ≤ 1:50 as determined by ELISA binding immunoassay.[4,9]
    - Patient must not have advanced SMA (i.e., complete paralysis of limbs, permanent ventilator dependence).

LENGTH OF INITIAL APPROVAL

- Evrysdi (risdiplam) or Spinraza (nusinersen): 12 months
- Zolgensma (onasemnogene): 1 month (1 infusion per lifetime). Reauthorization is not permitted.[9]

CRITERIA FOR RENEWAL APPROVAL FOR NUSINERSEN OR RISDIPLAM (Must meet the following criteria):

- The patient continues to meet initial criteria.
- Must meet one of the following:
    - Prescriber attests that the patient has achieved a new motor milestone or maintained muscle function compared to pretreatment baseline when they would otherwise be unexpected to. Must have one or more of the following:
        - Gains ability to sit without support ≥ 5 seconds.[10]
        - Gains ability to ambulate without support
    - Prescriber submits post-treatment documentation with the most recent results (< 1 month prior to request) documenting a positive clinical response from pretreatment baseline status demonstrated by at least one of the following:[8-10]
        - Hammersmith Infant Neurological Exam (HINE) (infant to early childhood):
            - Improvement or maintenance of previous improvement of at least 2 point (or maximal score) increase in ability to kick or Improvement or maintenance of previous improvement of at least 1-point increase in any other HINE milestone (e.g., head control, rolling, sitting, crawling, etc.).
        - Hammersmith Functional Motor Scale Expanded (HFMSE):
            - Improvement or maintenance of previous improvement of at least a 3-point increase in score from pretreatment baseline.
        - Upper Limb Module (ULM) Test (Non-ambulatory) or revised Upper Limb Module (RULM) Test (Non-ambulatory)
            - Improvement or maintenance of previous improvement of at least a 2-point increase in score from pretreatment baseline.
        - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)
            - Improvement or maintenance of previous improvement of at least a 4-point increase in score from pretreatment baseline.
        - Motor Function Measure 32 (MFM32):
            - Improvement or maintenance of previous improvement of at least a 3-point increase in score from pretreatment baseline.[10]
- Dosing must not exceed the FDA-approved dose as listed below in Table 1.

LENGTH OF RENEWAL APPROVAL: 12 months

FOR DRUGS THAT HAVE A CURRENT PA REQUIREMENT, BUT NOT FOR THE NEWLY APPROVED INDICATIONS, FOR OTHER FDA-APPROVED INDICATIONS, AND FOR CHANGES TO AGE REQUIREMENTS NOT LISTED WITHIN THE PA CRITERIA:
THE PA REQUEST WILL BE REVIEWED BASED UPON THE FOLLOWING PACKAGE INSERT INFORMATION: INDICATION, AGE, DOSE, AND ANY PRE-REQUISITE TREATMENT REQUIREMENTS FOR THAT INDICATION.

Notes:

- Efficacy of risdiplam in pre-symptomatic SMA patients is actively being studied.[11]

Table 1. FDA-approved age and dosing limits for SMA Agents.[8-10]

Agents	Indication(s)	Age	Dosing Limits
Antisense Oligonucleotides			
Nusinersen (Spinraza®)	Treatment of spinal muscular atrophy	Newborn - adult	4 Loading doses: 12 mg intrathecally. The first 3 loading doses should be administered at 14- day intervals; the 4th loading dose should be administered 30 days after the 3rd dose. Maintenance dose: 12 mg intrathecally administered once every 4 months.
Adeno-associated Virus Vector-based Gene Therapy			
Onasemnogene (Zolgensma®)	Treatment of spinal muscular atrophy	< 2 years	1.1×10^{14} vector genomes (vg) per kg of body weight.
Survival of Motor Neuron 2 (SMN2)-Directed RNA Splicing Modifier			
Risdiplam (Evrysdi™)	Treatment of spinal muscular atrophy	≥ 2 months	2 months to < 2 years of age: 0.2 mg/kg orally once daily. ≥ 2 years and weighing < 20 kg: 0.25mg/kg orally once daily. ≥ 2 years and weighing ≥ 20 kg: 5 mg orally once daily.

Table 2. Types of spinal muscular atrophy (SMA).[3]

SMA Type	Highest motor function without treatment*
1	Unable to sit independently
2	Able to sit, never able to walk independently
3	Able to walk independently

*SMA Types are classified based on the highest motor milestone attained.[3]

References:

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2. Mercuri, Eugenio, et al. "Nusinersen versus sham control in later-onset spinal muscular atrophy." New England Journal of Medicine 378.7 (2018): 625-635.

3. Evidence in focus: Nusinersen use in spinal muscular atrophy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018; 91:923-33. Available at https://n.neurology.org/content/91/20/923.long. Accessed on 5/31/19.
4. Mendell JR, Al-zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. N Engl J Med. 2017;377(18):1713-1722.
5. Kirschner, Janbernd, et al. "European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy". Eur J Paediatr Neurol. July 9, 2020, [ePub ahead of print]. Available at https://www.ejpn-journal.com/article/S1090-3798(20)30142-2/fulltext. Accessed on 8/26/2020.
6. NCT02908685, FIREFISH study. Available at https://clinicaltrials.gov/ct2/show/NCT02908685.
7. Frongia, A.L. et al. "Salbutamol tolerability and efficacy in patients with spinal muscular atrophy type II." Neuromuscul Disord 2019; 29(7):517-524. Available at https://www.nmd-journal.com/article/S0960-8966(18)30544-3/fulltext. Accessed on 8/31/2020.
8. Spinraza (nusinersen) [prescribing information]. Cambridge, MA: Biogen; June 2020.
9. Zolgensma (onasemnogene abeparvovec) [prescribing information]. Bannockburn, IL: AveXis, Inc; May 2019.
10. Evrysdi (risdiplam) [prescribing information]. South San Francisco, CA: Genentech, Inc; August 2020.
11. NCT03779334, RAINBOWFISH study. Available at https://clinicaltrials.gov/ct2/show/NCT03779334.

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DATE	DATE