Drug/Drug Class: Spinal Muscular Atrophy (SMA) Clinical Edit
First Implementation Date: April 22, 2021
Revised Date: April 21, 2022
Prepared for: MO HealthNet
Prepared by: MO HealthNet/Conduent
Criteria Status: ☒ Revision of Existing Criteria

Executive Summary

Purpose: Ensure appropriate utilization and control of agents for spinal muscular atrophy (SMA)

Why Issue Selected: Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disease with the most severe cases affecting infants and young children. The most common cause of SMA is the homozygous deletion or deletion and mutation of the alleles of the survival motor neuron (SMN) 1 gene on chromosome 5q. SMN protein is essential to motor neurons involved in ambulatory function, head and neck control, swallowing, and breathing. While the SMN1 gene produces most of the full-length SMN protein in the body, another gene, SMN2, also produces SMN protein. SMA is less severe in individuals who have more copies of the SMN2 gene because it can compensate for the SMN protein deficiency caused by the defect in the SMN1 gene. In the United States the incidence of SMA is approximately one in 11,000 live births or about 500 new SMA cases per year. Currently, there are two FDA approved maintenance therapies and one FDA approved one-time gene therapy for the treatment of SMA.

Spinraza® (nusinersen) is a SMN2-directed antisense oligonucleotide indicated for the treatment of SMA in pediatric and adult patients. Spinraza was the first FDA approved treatment for SMA, approved in December 2016. Spinraza alters the splicing of the SMN2 gene increasing the production of SMN2 protein which can compensate for the deficiency of SMN1 protein. Spinraza is a maintenance medication, administered intrathecally. The first year of treatment includes a total of 6 doses; the first 3 doses are given 14 days apart, the 4th dose is given 30 days after the 3rd dose, and then maintenance therapy is given every 4 months thereafter.

Evrysdi® (risdiplam) was FDA approved in August 2020 for the treatment of SMA in patients 2 months of age and older. Evrysdi is a SMN2-directed RNA splicing modifier that increases exon 7 inclusion in SMN2 mRNA transcripts and production of full-length SMN protein in the brain. Like Spinraza, Evrysdi is a maintenance medication; however, Evrysdi is the first medication which can be given at home for SMA patients, taken orally once a day.

In May 2019, the FDA approved Zolgensma® (onasemnogene abeparvovec-xioi), an adeno-associated virus vector-based gene therapy, for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene.
Zolgensma is the second gene therapy approved in the United States. Unlike Spinraza and Evrysdi, which provide maintenance therapy aimed at slowing the progression of the disease, current evidence and guidance position Zolgensma as a one-time, single-dose IV infusion treatment intended to repair the dysfunctional SMN1 gene.

### Setting & Population

- Drug class for review: Agents for spinal muscular atrophy (SMA)
- Age range: All appropriate MO HealthNet participants

### Approval Criteria

- Prescribed by or in consultation with a neurologist or other specialist in the treated disease state \( \text{AND} \)
- For Evrysdi and Spinraza:
  - Initial Approval Criteria:
    - Documentation of a confirmed diagnosis of SMA including genetic tests of 5q13 demonstrating:
      - Homozygous SMN1 gene deletion or mutation \( \text{OR} \)
      - Compound heterozygous SMN1 gene mutation \( \text{AND} \)
    - Sufficient number of copies of SMN2 gene defined as one of the following (either 2a or 2b) genetic tests demonstrating:
      - If a pre-symptomatic infant: \( \leq 3 \) copies of SMN2 gene \( \text{OR} \)
      - If a symptomatic patient:
        - \( \geq 2 \) copies of SMN2 gene \( \text{AND} \)
        - Documentation of age of onset of symptoms \( \text{AND} \)
    - Clinical baseline documentation received:
      - For all participants: pulmonary status (tracheostomy, hrs of ventilation, CPAP, etc.) \( \text{AND} \)
      - For participants aged < 3 years: Hammersmith Infant Neurological Exam-Part 2 (HINE-2) \( \text{OR} \)
      - For participants aged \( \geq 3 \) years: Hammersmith Functional Motor Scale Expanded (HFMSE) \( \text{AND} \)
      - Motor Function Measure 32 (MFM-32) \( \text{OR} \)
      - For ambulatory patients: 6 Minute Walk Test (6MWT) \( \text{OR} \)
      - For non-ambulatory patients: Revised Upper Limb Module (RULM) \( \text{Score} \)
    - For Spinraza only: complete blood count, coagulation status, urine protein, serum electrolytes including bicarbonate, liver and renal function tests
    - For Evrysdi only:
      - Participant aged 2 months and older \( \text{AND} \)
      - Participant is currently not pregnant \( \text{AND} \)

### Program-Specific Information:

<table>
<thead>
<tr>
<th>Date Range FFS 10-01-2020 to 9-30-2021</th>
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<tbody>
<tr>
<td>Drug</td>
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<tr>
<td>EVRYSDI 60 MG/80 ML</td>
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<tr>
<td>SPINRAZA 12 MG/5 ML VIAL</td>
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<tr>
<td>ZOLGENSMA</td>
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| Type of Criteria: | ☒ Increased risk of ADE | ☐ Preferred Drug List |
|                  | ☒ Appropriate Indications | ☒ Clinical Edit       |

| Data Sources:     | ☐ Only Administrative Databases | ☒ Databases + Prescriber-Supplied |
- Participant (female of appropriate age) must utilize concurrent birth control methods during and for 1-month post-treatment
  - Initial approval is for 6 months
- Renewal Approval Criteria:
  - Documented compliance on current therapy regimen AND
  - Documentation of benefit from therapy:
    - Improvement or maintenance of functional status from baseline functional tests (HFMSE or HINE-2, Pulmonary status, and MFM-32, 6MWT, or RULM) OR
    - Achievement and maintenance of new motor milestones from pretreatment baseline functional tests (HFMSE or HINE-2 and Pulmonary status) OR
    - Less than expected decline in functional ability or symptoms of disease as described by at least 1 of the following:
      - HFMSE: at least 3 points increase in score from pretreatment baseline
      - HINE-2 demonstrates:
        - Patient has demonstrated improvement in more categories than decline AND
        - At least 2 points (or maximum score) in ability to kick OR
        - At least 1 point in any other HINE milestone (head control, rolling, sitting, crawling, etc.)
      - MFM-32: at least 1 point increase in score from pretreatment baseline
      - For ambulatory patients 6MWT demonstrates at least a 30 meter increase from pretreatment baseline
      - For non-ambulatory patients RULM demonstrates at least a 2 point increase in score from the pretreatment baseline
  - For Spinraza:
    - Absence of unacceptable toxicity from the drug (examples of unacceptable toxicity include serious infections, fatal glomerulonephritis, thrombocytopenia, etc.) AND
    - Maintenance dosing is every 4 months
  - Renewal request, including documentation, is required every 12 months
- For Zolgensma:
  - Participant aged < 2 years AND
  - Documented diagnosis of SMA with bi-allelic mutations in the SMN1 gene AND
  - Documented anti-AAV9 antibody titers of ≤ 1:50 measured by ELISA at time of treatment AND
  - Documented completion of all required baseline assessments:
    - Liver function tests (AST, ALT, total bilirubin, and prothrombin time) AND
    - Serum creatinine AND
    - Complete blood count (CBC) including hemoglobin and platelets AND
    - Troponin-I levels

**Denial Criteria**

- Therapy will be denied if all approval criteria are not met
- For Evrysdi:
  - Documented diagnosis of hepatic impairment
  - Concurrent utilization with MATE transporters (i.e., metformin, cimetidine, acyclovir), Spinraza, or Zolgensma
- For Zolgensma:
  - Previous claim for Zolgensma at any time
  - Concurrent utilization with Spinraza or Evrysdi
  - Active viral or bacterial infection (including Hepatitis B, Hepatitis C, HIV, Zika virus, gastroenteritis, otitis media, bronchiolitis, etc.)
  - Concomitant illness that may create unnecessary risks for gene replacement therapy such as:
    - Major renal or hepatic impairment
    - Known seizure disorder
    - Diabetes mellitus
- Idiopathic hypocalcuria
- Symptomatic cardiomyopathy

### Required Documentation

- **Laboratory Results:** X
- **Progress Notes:** X
- **MedWatch Form:**
- **Other:** X

### Disposition of Edit

- Denial: Exception code “0682” (Clinical Edit)
- Rule Type: CE

### Default Approval Period

6 months

### References

- RS Finkel et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscular Disorders 28 (2018) 197–207. https://doi.org/10.1016/j.nmd.2017.11.004