Molina Clinical Policy
Spinraza (nusinersen): Policy No. 293
Last Approval: 8/9/2023
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Spinal muscular atrophy (SMA) is a rare, autosomal recessive, neurodegenerative disorder caused by deletions or loss-of-function mutations in the survival motor neuron 1 (SMN1) gene, resulting in survival motor neuron (SMN) protein deficiency. SMA is characterized by loss of motor neurons in the spinal cord and brainstem, resulting in gradual muscle atrophy and weakening. While SMA is caused by a mutation or deletion in the SMN1 gene, the clinical severity of SMA is correlated with several factors including age at disease onset, milestones reached, and the number of survival motor neuron 2 (SMN2) gene copies present. The primary gene responsible for the production of functional SMN protein is SMN1. There is also a minor contribution from SMN2, a paralogous copy of SMN1. Although SMN2 only contributes a small amount of SMN protein, when multiple copies of SMN2 are present, (typically three or more) SMA disease course is somewhat attenuated. SMN2 can be found in 0-8 copies in one individual (Vitali, 1999). The SMN1 and SMN2 genes have recently been identified as potential therapeutic targets for SMA. **Nusinersen** is an antisense oligonucleotide (ASO) agent that promotes SMN protein production by modifying SMN2 splicing resulting in increased SMN2 contribution to the pool of SMN protein.

SMA affects around one in every 11,000 births in the United States. It is the largest genetic cause of infant mortality and produces a variety of disabilities in adolescents and adults (Cure SMA, 2021). The severity of the disease varies greatly, ranging from infantile onset with progressive paralysis in the first months of life and death by 2 years of age (Type 1) to a mild, adult-onset type with a slow rate of progression (Type 4). SMA is divided into five types: Type 0, 1, 2, 3, and 4, with Type 0 representing the most severe disease (infants who are not carried to term or die soon after birth) and Type 4 representing the least severe (patients with normal life expectancy). The disease progresses regardless of type, and patients with SMA types 1, 2, and 3 are at high or moderate risk of developing respiratory insufficiency, which may necessitate mechanical ventilation. Prior to the approval of disease-modifying therapy, only supportive care interventions, such as pulmonary, orthopedic, gastrointestinal, and nutritional management, were available to manage the complications of SMA disease progression.

Spinraza is indicated for the treatment of SMA in pediatric and adult patients. At the time of FDA approval, Spinraza was only studied in infantile onset (Type 1), symptomatic infants less than 7 months of age at the time of first dose (FDA approval: 2016). In spite of this, Spinraza was broadly approved by the FDA for "the treatment of SMA in pediatric and adult patients" regardless of SMA type classification (e.g., phenotype or age of onset) because the FDA expected that extrapolation of efficacy and clinical benefit to the later-onset SMA subtype was plausible. Clinical data from the pivotal randomized sham-procedure controlled phase 3 research in later-onset SMA (presumably Type II or III) was not assessed by the FDA as the trial was still underway.

Spinraza is administered intrathecally directly into the central nervous system to target motor neurons because ASOs do not adequately penetrate the blood brain barrier. The treatment course consists of loading phase with three injections given every two weeks and the fourth injection 4 weeks after the third. Maintenance therapy consists of repeat injections at every 4-month intervals. The risks of therapy include, thrombocytopenia, coagulation problems, renal toxicity, respiratory tract infections and constipation. Platelet count, prothrombin time, activated partial thromboplastin time, and quantitative spot urine protein testing are therefore recommended at baseline and before each dose.

COVERAGE POLICY

Spinraza (nusinersen) for the treatment of SMA **may be considered medically necessary** when **ALL** of the following clinical criteria are met:

1. Diagnosis of SMA Type 1, 2 or 3

AND

2. Genetic testing documentation of mutation or deletion of genes in chromosome 5q resulting in **ONE** of the following:
   a. Homozygous gene deletion or mutation in the SMN1 gene (e.g., absence of the SMN1 gene; homozygous deletion of exon 7 at locus 5q13; biallelic mutations of exon 7); **OR**
   b. Compound heterozygous mutation in the SMN1 gene [e.g., deletion of SMN1 exon 7 (allele 1) and a pathogenic mutation in the SMN1 gene (allele 2)]

AND

3. Member has at least 2 copies of the SMN2 gene

   Informational Note: Laboratories offering genetic testing for SMA may be located at the Genetic Testing Registry. While the approved labeling of Spinraza does not require SMN2 copy number analysis, the ENDEAR trial required homozygous deletion or mutation in the SMN1 gene AND 2 copies of the SMN2 gene (98% of participants had 2 copies of SMN2 genes, while others had 3 or 4 copies). A higher number of SMN2 copies is correlated with less severe disease and has not been established whether patients with less than 2 copies of SMN2 genes would make sufficient SMN protein to mitigate the symptoms of SMA.

AND

4. Member is **not** dependent on either of the following:
   a. Invasive ventilation (for not more than 16 hours per day) or tracheostomy; **OR**
   b. Use of non-invasive ventilation beyond naps and nighttime sleep, or Non-invasive ventilation for more than 12 hours per day

   NOTE: Refer to 'Coverage Exclusions' section for additional information

AND

5. Member has not previously received gene replacement therapy for the treatment of SMA, AND will not be receiving other SMA disease-modifying treatments concurrently (e.g., Zolgensma, Evrysdi)

AND

6. Confirmation that the member is not currently enrolled in or participating in a clinical trial for nusinersen.

   NOTE: Requests will not be authorized for members currently enrolled in clinical trials for Spinraza. In such cases, the drug manufacturer should provide continued coverage and be monitored per protocols in place by the applicable Institutional Review Board.

AND

7. Baseline motor function assessment using at least **ONE** of the following assessment tools† appropriate for participant age and motor function (prior to initial therapy):
   a. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (†CHOP INTEND)
   b. Hammersmith Functional Motor Scale Expanded (†HFMSE)
   c. Hammersmith Infant Neurologic Exam Part 2 (HINE-2): Infant to early childhood
   d. 6-minute walk test (6MWT): Ambulatory patients
   e. Upper Limb Module (ULM) or Revised ULM (RULM) score: Non-ambulatory patients

   †Measures have been developed and validated specifically for SMA populations

Refer to Appendix 2: Assessment Tools for Motor Development (SMA Outcome Measures)

AND

8. Baseline (pre-treatment) laboratory tests *within 30 days* of request (obtain prior to each dose as appropriate):
   a. Quantitative spot urine protein testing (For urinary protein concentration >0.2 g/L, consider repeat testing and further evaluation); **AND**
   b. Coagulation status: Prothrombin time; activated partial thromboplastin time; **AND**
   c. Platelet count (platelet count > 50,000 cells per microliter)

AND

9. Prescriber agrees to submit a clinical progress report including treatment outcomes for the member every 6 months following initial dosing, and is required for continuation of treatment requests

CONTINUATION OF THERAPY

1. Criteria for initial therapy was met; **AND**

2. Continuation of treatment requires an office visit and re-assessment for this condition to determine if continuation of treatment with requested medication is medically necessary; **AND**

3. *Documentation of disease stabilization or improvement by at least **ONE** of the following outcome measures within 30 days of request
   a. CHOP-INTEND: At least 4-point increase from pretreatment baseline; **OR**
   b. HFMSE: At least 3-point increase from pre-treatment baseline; **OR**
   c. HINE-2: At least 2-point (or maximal score) increase in ability to kick OR at least 1-point increase in any other HINE milestone (e.g., head control, rolling, sitting, crawling, etc.), excluding voluntary grasp; **OR**
   d. 6MWT: At least 30 meters increase from pretreatment baseline; **OR**
   e. ULM or RULM score: At least 2-point increase from pretreatment baseline; **OR**
   f. Achievement and maintenance of *new* motor milestone from pretreatment baseline that is otherwise not expected, OR Improvement in *more categories* of motor milestones than worsening, OR Improvement or maintenance of *previous improvement* from pretreatment baseline; **OR**
   g. Member remains permanently ventilator-free.

   *Submission of an Assessment Tool for Motor Development should be the same assessment performed at baseline, appropriate for participant age and motor function. *Refer to Appendix 2: Assessment Tools for Motor Development (SMA Outcome Measures)*.

AND

4. Adherence to the dosing regimen, as specified in the FDA-approved labeling, is confirmed through pharmacy/medical claims for services, laboratory claims or submission of progress notes. Repeated non-adherence may result in denial of renewal request

   NOTE: Members may have an interruption in therapy for a planned surgery or during the management of a systemic infection, in which case, will be considered and may require additional information or peer-to-peer.

   NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when noted or demonstrated during authorization.

AND

5. Submission of the following labs (dated within the past 30 days of request):
   a. Quantitative spot urine protein testing; **AND**
   b. Platelet count; **AND**
   c. Prothrombin time (activated partial thromboplastin time).

AND

6. Member is NOT dependent on either of the following:
   a. Invasive ventilation or tracheostomy; **OR**

b. Use of non-invasive ventilation beyond naps and nighttime sleep.

AND

7. Member has not previously received gene replacement therapy for the treatment of SMA, **AND** will not be receiving other SMA disease-modifying treatments concurrently (e.g., Zolgensma, Evrysdi).
   Refer to 'Coverage Exclusions' section for additional information.

AND

8. Confirmation that the member is not currently enrolled in or participating in a clinical trial for nusinersen.

   NOTE: Requests will not be authorized for members currently enrolled in clinical trials for Spinraza. The drug manufacturer should provide continued coverage and be monitored per protocols in place by the applicable Institutional Review Board.

LIMITATIONS AND EXCLUSIONS

The following are **considered contraindications/exclusions/discontinuations** based on insufficient evidence:

1. Hypersensitivity to nusinersen or any component of the formulation or its inactive ingredients (calcium chloride dihydrate, magnesium chloride hexahydrate, potassium chloride, sodium chloride, sodium phosphate dibasic anhydrous, sodium phosphate monobasic dihydrate, and water for injection)
2. Respiratory failure: Member has received a tracheostomy or become ventilator dependent
3. Previously received gene replacement therapy for the treatment of SMA, OR will be receiving other SMA disease-modifying treatments concurrently (e.g., Zolgensma, Evrysdi), OR Current enrolled in a clinical trial for SMA treatment
4. Medical condition(s) that may affect patient safety or the ability to carry out lumbar puncture procedures or outcome measure testing, including but not limited to:
   a. Untreated or inadequately treated active infection, or presence of infected skin at the target puncture site
   b. History of brain or spinal cord disease or abnormalities, tumors, severe contractures, or severe scoliosis
   c. Implanted shunt for the drainage of cerebrospinal fluid or an implanted CNS catheter
   d. History of bacterial meningitis
   e. Prior injury (e.g., upper or lower limb fracture) or surgical procedure from which the subject has not fully recovered or achieved a stable baseline
   f. Presence of unequal pressures between the infratentorial and supratentorial compartments
   g. Coagulopathy, brain abscess, or increased intracranial pressure (Relative contraindications for lumbar puncture)

Discontinue therapy if any of the following is applicable:

5. Intolerable adverse effects or toxicity (e.g., coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia and renal toxicity, including potentially fatal glomerulonephritis)
6. Persistent and uncorrectable problems with adherence to treatment
7. Poor response to treatment as evidenced by physical findings and/or clinical symptoms as documented by outcome measures, or other motor function assessment tool

The following are considered **experimental, investigational and unproven** based on insufficient evidence:

1. Any indications other than those listed above

2. SMA Type 0 or 4
   - Spinraza has only been studied in patients with SMA types 1-3 which make up approximately 95% of all SMA cases. SMA type 4 is usually later onset (often after age 30) and patients can achieve motor milestones and maintain mobility throughout life. There is insufficient evidence to support safety and efficacy of nusinersen in Type 0 or 4. There are currently no published trials or interim studies to support the safety and efficacy of nusinersen in SMA Type 0 and 4 (adult onset).

3. Adolescents or adults 15 years of age and older

There are limited studies supporting SMA patients 15 years of age and older:

- There are no published phase 3 trials which include patients 15 years of age and older (ENDEAR: younger than 6 months of age at SMA symptom onset and younger than 7 months of age (210 days) at screening; CHERISH: males/females between 2 and 12 years old at screening).
- There is a lack of evidence from published interim analysis as there are no open-label studies that evaluated patients 15 years of age and older. The ENDEAR phase 3 study, the basis for the FDA's approval of Spinraza, supported by smaller open-label, uncontrolled studies include patients with infantile-onset and childhood SMA, aged 2 to 14 (types 2 and 3 SMA). Furthermore, data from uncontrolled, open-label studies evaluating nusinersen for symptomatic patients were limited to patients ages 30 days to 15 years and pre-symptomatic patients ages 8 to 42 days were generally supportive of the clinical benefit that was seen in the ENDEAR trial (Biogen, 2016; UTD 2021).

4. SMA patients requiring permanent ventilation
   - Clinical studies have shown that Spinraza reduces the risk of permanent ventilation (defined as tracheostomy or 16 or more hours of ventilator support per day continuously for at least 2 weeks in the absence of an acute reversible illness); however, Spinraza has not been studied in patients who already require permanent ventilation in any sub-type of SMA.
   - There is a lack of evidence demonstrating the safety and efficacy of Spinraza in patients who already require permanent ventilation in any sub-type of SMA. Patients in the ENDEAR trial did not require permanent ventilation at baseline (permanent ventilation was defined as the need for 16 hours or more of continuous ventilator support per day for 21 or more consecutive days, in the absence of an acute reversible event, or if the patient required tracheostomy).

5. Concurrent use of Spinraza with gene replacement therapy (e.g., Zolgensma, Evrysdi) for treatment of SMA
   - Combined treatment with Zolgensma and nusinersen has recently been investigated in a small group of patients, although the long-term benefit is still unclear (Lee et al. 2021). Longer-term follow-up data, especially in the treatment of pre-symptomatic patients, should be accumulated to assess the efficacy and risks of combination therapy.
   - A phase 4 study, RESPOND, is a two-year, open-label study to evaluate the efficacy and safety of Spinraza in SMA patients previously treated with Zolgensma who still have unmet clinical needs. RESPOND will be conducted at approximately 20 sites worldwide and aims to enroll 60 children up to 3 years old who are determined by the investigator to have the potential for additional clinical improvement after receiving Zolgensma. (NCT04488133). **Estimated Study Completion Date: September 4, 2024**
   - A group of European neuromuscular experts agreed by 100% consensus that 'Until now there is no published evidence that combination of two disease modifying therapies (e.g., gene therapy and nusinersen) is superior to any single treatment alone' (2020 European Neuromuscular Expert Ad-Hoc Consensus Statement on Gene Replacement Therapy for SMA).

6. Concomitant or previous participation in clinical trials for SMA treatment, SMN2-targeting ASO, SMN2 splicing modifier or gene therapy study

DURATION OF APPROVAL: Initial authorization: 6 months (5 doses); Continuation of therapy: 6 months

PRESCRIBER REQUIREMENTS: Prescribed by, or in consultation with, a board-certified pediatric neuromuscular specialist, pediatric neurologist, or neurologist with experience in the diagnosis and management of SMA

AGE RESTRICTIONS: 15 years of age or younger at initiation of treatment

DOSING CONSIDERATIONS: Loading dose: 12 mg intrathecally once every 14 days for 3 doses; then 12 mg intrathecally once 30 days after the 3rd dose. Maintenance dosage: 12 mg intrathecally once every 4 months.

QUANTITY LIMITATIONS

1. Maximum dose: 12 mg (5 mL) intrathecally per administration; **AND**
2. Initial authorization: 4 loading doses; **AND**
   - Loading dose: initiate with 4 loading doses (12mg intrathecally); the first 3 doses should be administered at 14-day intervals, followed by the 4th loading dose 30 days later.

3. Continuation of treatment: 3 maintenance doses every 12 months
   - Maintenance dose: a maintenance dose (12mg intrathecally), should be administered once every 4 months following the last loading dose.

ADMINISTRATION:
1. Administered by, or under the direction of healthcare professionals experienced in performing lumbar punctures using aseptic technique; consider sedation and ultrasound or other imaging techniques to guide intrathecal administration
2. Refer to MHI Policy & Procedure: *Specialty Medication Administration Site of Care Policy: MHI Pharm 11*.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DRUG INFORMATION

ROUTE OF ADMINISTRATION: For intrathecal use only

DRUG CLASS: Musculoskeletal Agents; Antisense Oligonucleotide

FDA-APPROVED USES: SMA

COMPENDIAL APPROVED OFF-LABELED USES: None

SUMMARY OF MEDICAL EVIDENCE

Intrathecal nusinersen therapy was found to be safe and tolerated in early clinical trials, with evidence of therapeutic benefit (Chiriboga et al. 2016; Finkel et al. 2016) Nusinersen was approved for marketing by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) primarily based on an interim analysis of the multicenter, double-blind ENDEAR trial. The study included infants with SMA that were 7 months or younger at the time of the screening trial, excluding those who had peripheral oxygen desaturation (i.e., oxygen saturation below 96 percent without ventilation support). Randomly, infants were assigned intrathecal nusinersen therapy or a sham procedure in a ratio of 2:1 (control). In an interim analysis of 82 eligible patients enrolled for at least six months (Finkel et al. 2017), improvement in motor milestones (e.g., head control, sitting, kicking in supine position, rolling, crawling, standing, and walking) as measured by the Hammersmith Infant Neurological Examination (HINE) was observed in 21 of 51 (41%) infants treated with nusinersen compared to 0 of 27 (0%) infants treated with a sham procedure. In addition, results from uncontrolled, open-label studies examining nusinersen in symptomatic (30 days to 15 years) and presymptomatic (8 to 42 days) patients confirmed the therapeutic benefit demonstrated by the ENDEAR trial (Finkel et al. 2017; ENDEAR Study Group; NCT02193074).

ENDEAR (Finkel et al., 2017) was a phase 3 randomized, double-blind, sham-controlled, safety and effectiveness trial of Spinraza in infants with SMA. A homozygous deletion or mutation in the SMN1 gene was documented genetically in all eligible subjects. In addition, they had two copies of the SMN2 gene, exhibited clinical symptoms consistent with SMA by 6 months of age, were 7 months of age or younger during screening, and did not exhibit low peripheral oxygen saturation. The primary objectives were a motor milestone response, as determined by the Hammersmith Infant Neurological Examination (HINE), and event-free survival (time to death or the use of permanent assisted ventilation). For the first primary endpoint, participants were considered to have a motor milestone response if they met both of the following criteria: improvement in at least 1 category on the HINE (i.e., an increase in the score for head control, rolling, sitting, crawling, standing, or walking of 1 point, or achievement of the maximum score for kicking) and more categories with improvement than categories with worsening. An interim analysis was conducted on 78 patients who had been enrolled for at least six months: 51 in the Spinraza group and 27 in the control group. The study indicated a favorable benefit–risk evaluation for Spinraza, which led to the premature end of the trial. In the final analysis, 39% of individuals in the Spinraza group and 68% of participants in the control group had died or were receiving permanent assisted ventilation. In the control group, the median time

to death or the use of permanent assisted ventilation was 22.6 weeks, whereas in the Spinraza group, this point was never reached. The risk of death or the need for permanent assisted ventilation was reduced by 47% in the Spinraza group compared to the placebo group.

To date, the benefits of Spinraza have been demonstrated in two major phase-3 studies: the ENDEAR trial, which compared nusinersen to a sham control in infantile-onset SMA, and the Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy trial, which compared nusinersen to a sham control in patients with later-onset SMA (CHERISH trial).

In the final analysis of the ENDEAR trial, 37 of 73 (51%) infants treated with nusinersen demonstrated progress in motor milestones, compared to 0 of 37 (0%) infants treated with a placebo (Finkel et al. 2017). In the nusinersen therapy group, the motor milestones attained were head control (22%), rolling over (10%), sitting independently (8%) and standing (1%). No infants reached motor milestones in the group that received a sham treatment. In the nusinersen group, fewer infants died or required permanent supported ventilation than in the placebo group (39 versus 68%).

CHERISH. A positive interim analysis of 126 patients (84 assigned to nusinersen treatment and 42 to sham control) in the double-blind CHERISH trial, which enrolled children with SMA aged 2 to 12 years, supports the evidence of benefit for older children with SMA (Mercuri et al. 2018). Children who were eligible for the study had symptoms that began before the age of 6 months, could sit but not walk independently, and had a life expectancy of more than two years. Respiratory failure (requiring invasive or noninvasive ventilation for more than 6 hours each 24-hour period), the requirement for a gastric feeding tube for the majority of feeds, severe contractures or scoliosis, or medical incapacity were also exclusion factors (e.g., wasting or cachexia). After a predetermined interim analysis, the trial was terminated early for benefit. At month 15 of treatment, patients receiving nusinersen had a mean improvement of 3.9 points on the Hammersmith Functional Motor Scale Expanded (HFMSE), compared to a decline of 1.0 points in the control group, for a mean difference of 4.9 points, where a difference of ≥ 3 points was considered clinically significant (Mercuri et al. 2018).

A prospective observational cohort study of patients ages 16 to 65 years old who received nusinersen and had complete data available at 6 months (n = 124), 10 months (n = 92), and 14 months (n = 57) noted evidence of benefit for adults with SMA (Hagenacker et al. 2020). Nusinersen treatment resulted in a clinically meaningful improvement, defined as an increase of 3 points or more in the HFMSE score compared to baseline, in 28% of patients after 6 months, 35% after 10 months, and 40% after 14 months.

Anti-Drug Antibodies (ADAs). Nusinersen is a large molecule medication with the potential to cause ADAs to develop. According to the labeling, 4% of patients who were tested for antibodies had persistent ADAs, and there are insufficient data to determine if ADAs have an effect on clinical response, side events, or the pharmacokinetic profile of nusinersen (Prescribing Information, 2020). The impact of this on treatment response is unclear at this time, however it is probable that certain ADAs are neutralizing antibodies that reduce treatment efficacy. Prescribers may consider switching to a different therapy if response has waned and ADAs have been detected or suspected.

National and Specialty Organizations

The **American Academy of Neurology** published a systematic review of the evidence for the use of nusinersen in SMA (2018) with the endorsement of the American Academy of Pediatrics. The systematic review included 4 published clinical trials, 3 of which were rated above Class IV (Studies not meeting Class I, II, or III criteria including consensus or expert opinion).

- In infants with homozygous deletions or mutations of SMN1, nusinersen improves the probability of permanent ventilation-free survival at 24 months vs a well-defined historical cohort: Class III evidence

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.

- In term infants (gestational age 37-42 weeks) with SMA and 2 copies of SMN2, treatment with nusinersen started in individuals younger than 7 months results in a better motor milestone response and higher rates of event-free survival than sham control (after at least 6 months of treatment). (ENDEAR; Finkel, et al. 2017)

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population.

- In children aged 2–12 years with SMA symptom onset after 6 months of age, nusinersen results in greater improvement in motor function at 15 months than sham control. Nusinersen was safe and well-tolerated. (CHERISH; Mercuri, et. al. 2018)

Cure SMA Working Group. The 2018 Cure SMA Working Group treatment algorithm emphasizes early intervention through newborn screening (Glascock et al. 2018). The group had the following recommendations:

- Develop reliable and proven screening tools to treat pre-symptomatic patients, who may be more responsive than symptomatic patients;
- For patients with SMA Types 2 or 3 and 3 or fewer copies of the SMN2 gene, immediate treatment with a disease-modifying therapy and referral to both a neuromuscular specialist and a geneticist is recommended;
- For those with only 1 copy of SMN2 who are symptomatic at birth, the group recommends that the attending physician determine whether the patient and family would benefit from treatment;

1. Patients with 4 copies of SMN2 should be frequently checked for symptoms and referred to a geneticist to determine the exact number of SMN2 copies; nevertheless, the working group does not propose urgent treatment with a disease-modifying drug.

Cure SMA reconvened the interdisciplinary working group in September 2019 to reevaluate the treatment protocol for newborns with SMA identified by newborn screening in light of new experience and therapeutic approaches with the following amendments or recommendations (Glascock et al. 2019):

- Revised position to suggest immediate therapy for newborns with SMA identified by NBS with 4 copies of SMN2.
- Revisited the previously published recommendation to wait to treat infants with 5 copies of SMN2 and unanimously voted to uphold the recommendation.
- The current laboratory tests for detecting SMN2 copy number have difficulties identifying large copy numbers of SMN2, and that many laboratories report findings as 4 or more SMN2 copies, without being able to provide an accurate number. Recognizing this, the working group advised further testing with a laboratory capable of determining the actual SMN2 copy number.

European Neuromuscular Expert Ad-Hoc Consensus Statement on Gene Replacement Therapy for SMA (2020). Following approval of Zolgensma by the EMA, a group of 13 European neuromuscular experts presented 11 consensus statements covering qualification, patient selection, safety considerations, and long-term monitoring (Kirschner et al. 2020). Over 95% was deemed 'strong consensus,' 75-95% 'consensus,' and 50-75% 'majority consensus.' Less than 50% approval meant 'no consensus.' Among the 11 consensus statements was one on combination therapy and a discussion of the rationale. The group stated the following with a 100% consensus: "Until now there is no published evidence that combination of two disease modifying therapies (e.g., gene therapy and nusinersen) is superior to any single treatment alone."

SUPPLEMENTAL INFORMATION

Antisense oligonucleotides (ASO) are synthetic single-stranded strings of nucleic acids that bind to precursor ribonucleic acid (pre-RNA) or messenger RNA (mRNA) to interfere with gene splicing, regulation of protein translation, or RNA/protein binding. The goal is to manipulate the SMN2 gene to produce higher amounts of functional SMN protein and correct the fundamental defect in SMA. (Tisdale, 2015)

APPENDIX 1: Classification of SMA
Historically, SMA had been classified into 5 subgroups based on age of onset and achieved milestones, types 0 (congenital) through IV (adult) [HRSA Final Report (v5.2) 2018]. However, due to development of disease-modifying treatments and the resulting dynamic clinical overlaps between subgroups an adjusted classification by maximal motor function (non-sitters, sitters, and walkers) may correlate with clinical care needs better (Mercuri et al. 2018; Finkel). In this system each subgroup comprises patients that either never achieve the ability to sit or walk or lose/achieve the respective ability during their lifetime (Butchbach ME 2016).

Individuals with 5q SMA have no functional SMN1 genes and rely on their copies of the SMN2 gene for all SMN protein production, which results in low levels of the SMN protein. The severity of disease varies between individuals in large part because of differences in SMN2 copy number. Individuals with SMA who have more copies of SMN2 genes generally have less severe forms of SMA as follows:

1. An individual with a single SMN2 gene and no copies of SMN1 is severely affected at birth;
2. Infants with SMA type 1 generally have 2 copies of SMN2;
3. Children with SMA type 2 usually have 3 copies of SMN2 and;
4. Those with SMA type 3 or SMA type 4 have more than 3 copies.

Although SMN protein is ubiquitously expressed, its absence in 5q SMA primarily affects motor neurons, though lesser effects have been documented in other tissues.

APPENDIX 2: Assessment Tools for Motor Development (SMA Outcome Measures)

CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders)
- Clinician-administered tool designed to evaluate motor function in infants with SMA
- Validated for use in SMA type 1 infants
- Includes 16 items: each of which is scored based on a 0 to 4-point scale (0 for no response, 1 for minimal, 2 for partial, 3 for nearly full, 4 for complete)
- Total scores range from 0 to 64 points; Higher scores indicate better function

HINE-2 (Hammersmith Infant Neurological Exam Section 2)
- Clinician-administered tool to evaluate motor function in children ages 2 to 24 months
- Assessment has been used for Type 1 SMA
- Measures achievement of 26 motor milestones in 8 main motor-milestone categories (voluntary grasp, kicking, head control, rolling, sitting, crawling, standing, and walking) with each having subcategories to track incremental changes in functional gain that leads up to achieving the milestone
- Maximum total score possible is 26; Higher scores indicate better function
- By 18 months, more than 90% of healthy toddlers can achieve each milestone

HFMSE (Hammersmith Functional Motor Scale-Expanded Test)
- Clinician-administered tool designed to measure motor function in children with later-onset SMA Type 2 and 3, including non-ambulatory and ambulatory patients
- Assessment includes 33 items total; per-item scores range from 0 (unable to perform activity) to 2 (able to perform activity without assistance or modification), with higher scores representing a higher motor ability
- Total scores range from 0 to 66 points; higher scores indicate better function; 3-point change is considered clinically significant
- Assessment employed in phase 3 CHERISH study for late-onset SMA; per study authors 'A change in the HFMSE score of at least 3 points is considered clinically meaningful.'

6MWT (6-Minute Walk Test)
- An objective evaluation of functional exercise capability in ambulatory patients with later-onset SMA
- Patient walks as far as possible in six minutes

Upper Limb Module (ULM)/Revised Upper Limb Module (RULM)
- ULM was developed to evaluate daily-life function in nonambulatory SMA patients. The original ULM was designed to evaluate upper limb function in non-ambulatory SMA patients, especially young children, and was previously validated for this population. It was changed and revised to RULM because of ceiling effects.
- A set of 19 tasks to measure motor function in non-ambulatory SMA patients, with a 3-point ordinal scale for each item: 0 (unable), 1 (able, with modification), and 2 (able, no difficulty), giving a maximum total score of 38. The patient chooses one arm with which to perform the tasks.

Reference: Clinical Review Report: Nusinersen (Spinraza): (Biogen Canada Inc.): Indication: Treatment of patients with 5q SMA [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018 Jan. Appendix 5, Validity of Outcome Measures. Available from: https://www.ncbi.nlm.nih.gov/books/NBK533982/

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology) Code

CPT	Description
96450	Chemotherapy administration, into CNS (e.g., intrathecal), requiring and including spinal puncture

HCPCS (Healthcare Common Procedure Coding System) Code

HCPCS	Description
J2326	Injection, nusinersen, 0.1 mg

AVAILABLE DOSAGE FORMS: 12 mg/5 mL solution (single dose vials) for intrathecal administration

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

8/09/2023 Policy reviewed. Updated references and coding. No change to coverage criteria.
8/10/2022 Policy revised. Updated summary of medical evidence and references. IRO Peer Review. 06/20/22. Practicing Physician. Board certified in Neurology. Notable revisions to coverage criteria include:
Removal of Hammersmith Functional Motor Scale (HFMS) as validation scale and use HFMSE (the validity and reliability of HFMSE in SMA 2 and 3 patients were confirmed in studies)
Addition of 'Criteria for initial therapy was met' in Continuation of Treatment criteria
8/11/2021 Policy revised. IRO Peer Review. 6/14/2021. Practicing Physician. Board certified in Neurology. Notable revisions include: updated 'Coverage Exclusions' section criterion on 'Concurrent use of Spinraza with gene replacement therapy for the treatment of SMA [e.g., Zolgensma (onasemnogene abeparvovec)], Added 'Evrysdi (risdiplam)'and informational notes supporting rationale. For congruency with existing criteria (#2) in 'Coverage Criteria for Initial Authorization' the following was added to Reauthorization/Continuation of Therapy section (#3 in 'Labs/Reports/Documentation required'): 'Member is not dependent on either of the following: Invasive ventilation or tracheostomy; or Use of non-invasive ventilation beyond naps and nighttime sleep'
Q4 2020 Policy revised. IRO Peer Review. 6/22/2020. Practicing Physician. Board certified in Neurology, Sleep Medicine. Notable revisions include: Revision of 'Respiratory Insufficiency' criterion from: Member must not currently require permanent ventilation defined by the need for continuous ventilator support (invasive or non-invasive ventilation) for greater than 16 hours during a 24-hour period; to: Member is not dependent on either of the following: 1) Invasive ventilation (for not more than 16 hours per day) or tracheostomy; or 2) Invasive ventilation (for not more than 16 hours per day) or tracheostomy; or 2) Use of non-invasive ventilation beyond naps and nighttime sleep, or Non-invasive ventilation for at least 12 hours per day
Q4 2019 Policy revised. IRO Peer Review. 9/10/2019. Practicing Physician. Board certified in Neurology, Sleep Medicine. Notable revisions include adding the following criterion in 'Exclusions' section: use of nusinersen after gene replacement therapy and concomitant use of nusinersen and onasemnogene abeparvovec (Zolgensma)
7/10/2018 Policy revised. IRO Peer Review: 5/2/2018. Practicing Physician. Board certified in Neurology, Sleep Medicine.
2/16/2017 New policy. IRO Peer Review: 2/13/2017. Practicing Physician. Board certified in Neurology, Pain Management.

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