Subject: Spinraza (nusinersen)	**Original Effective Date:** 2/16/2017
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. 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 (i.e., 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 document and provide the directive for all Medicare members.

Contents

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

This policy addresses Spinraza (nusinersen) for the treatment of **spinal muscular atrophy (SMA)**. Molina Healthcare reserves the right to update this Policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

SMA is a severe, inherited, progressive neuromuscular disease that causes devastating muscle atrophy and disease-related complications. It is the most common genetic cause of infant mortality and one of the most common rare diseases, affecting approximately one in 11,000 babies. SMA leads to the progressive loss of nerve cells in the spinal cord that control muscle movement. Depending on the type of SMA, an individual's physical strength and their ability to walk, eat or breathe can be significantly diminished or lost.

SMA is caused by a mutation in the survival motor neuron 1 (SMN1) gene that results in a deficiency of SMN protein. SMN protein is found throughout the body and increasing evidence suggests SMA is a multi-system disorder and the loss of SMN protein may affect many tissues and cells, which can stop the body from functioning.

Spinraza (nusinersen)

- A survival motor neuron-2 (SMN2)-directed antisense oligonucleotide indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients
- The first and only disease modifying agent approved for all phenotypes of SMA to treat both pediatric and adult patients. There are no other disease-modifying treatment options currently for SMA.
- Current treatment for patients with SMA is limited and generally consists of supportive care supportive/symptomatic treatments are available (e.g., respiratory management, nutritional support, management of orthopedic complications). Nusinersen treatment is not curative and does not restore normal motor function. Most SMA patients will continue to require orthopedic, nutritional, or pulmonary supportive care while on therapy with nusinersen.
- Administered via intrathecal lumbar puncture with topical anesthesia using standard techniques for infants; children older than 2 years of age may require sedation. Patients require 6 doses of nusinersen in the first year of treatment, then 3 doses yearly (administered 4 months apart) thereafter.
- The most common adverse reactions reported for nusinersen were upper respiratory infection, lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in nusinersen-treated patients. Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

FDA-Approved indication Based principally on the results of a planned interim analysis that was conducted in a subset of patients enrolled in a multicenter, double-blind, sham procedure-controlled phase 3 study (ENDEAR).[AHFS 2020]

ENDEAR was a multisite, randomized, double-blind, sham-controlled trial of patients with SMA type 1 and two copies of the SMN2 gene. The trial enrolled infants with SMA 7-months of age or younger and randomly assigned them to intrathecal nusinersen treatment or sham procedure (control) in a 2 to 1 ratio.

INTERIM EFFICACY ANALYSIS (ENDEAR) was conducted based on patients who had received at least 6 months (183 days) of treatment, withdrawn from the study, or died, and included a total of 82 eligible patients (56% female, 87% white, and 98% with 2 copies of the SMN2 gene). **Based on the positive results of the interim analysis, the ENDEAR study was terminated early and all patients were transitioned to active treatment with nusinersen.**

- Among the 82 patients who were included in the interim analysis, **40% (21 of 51) achieved a motor milestone response** (e.g., head control, sitting, kicking in supine position, rolling, crawling, standing, and walking) **compared with none of the patients in the control group (0 of 27)** as measured by the Hammersmith Infant Neurological Examination (HINE) (Finkel RS, et al. 2017).
- Motor function also was assessed by the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) as a secondary end point in this study; although the test was not statistically controlled for multiple comparisons, an improvement in CHOP-INTEND score (defined as an increase from baseline of at least 4 points) was achieved in 63% of patients in the nusinersen group compared with 3% of patients in the control group, and a worsening of the CHOP-INTEND score (defined as a decrease from baseline of at least 4 points) occurred in 4 and 40% of patients in the respective treatment groups.

- Five patients in the nusinersen group were able to sit unassisted compared to no patients in the control group. According to the investigators, this would be an extremely rare milestone in patients diagnosed with SMA type 1, although it is possible that some of those patients could have had SMA type 2.
- Patients transitioned to the open-label extension study **SHINE (ClinicalTrials.gov number, NCT02594124).**
- In addition, data from uncontrolled, open label studies evaluating nusinersen for symptomatic patients (ages 30 days to 15 years) and presymptomatic patients (ages 8 to 42 days) were generally supportive of the clinical benefit that was seen in the ENDEAR trial (Biogen Inc., 2017).

IN THE FINAL ANALYSIS (ENDEAR trial)

- **Improvement in motor milestones was noted in 37 of 73 (51%) infants treated with nusinersen, versus 0 of 37 (0%) of infants who received the sham procedure** [37 of 73 infants (51%) vs. 0 of 37 (0%)] (Finkel RS, et al. 2017).
- In the nusinersen treatment group, motor milestones achieved included head control (22%), rolling over (10%), sitting independently (8%), and standing (1%). In the sham procedure group, no infants achieved motor milestones.
- The likelihood of **event-free survival was higher in the nusinersen group** than in the control group. The proportion of **infants who died or received permanent assisted ventilation was lower in the nusinersen group** compared with the sham group (39 versus 68%, hazard ratio 0.53, 95% CI 0.32-0.89).
- The likelihood of **overall survival was higher in the nusinersen group than in the control group** (hazard ratio for death, 0.37; P = 0.004), and **infants with a shorter disease duration** at screening were more likely than those with a longer disease duration to benefit from nusinersen.

Type I (Infantile-Onset) SMA

The evidence supporting efficacy for children with SMA Type I includes **2 randomized, double-blind, controlled trials and 1 single-arm open-label study (NURTURE),** including both early, *asymptomatic infants with SMA type I* (NURTURE) and *young symptomatic infants (less than 7 months old) with SMA type I* (ENDEAR study).

- Published phase 3 trials, ENDEAR and CHERISH, and interim data from the NUTURE study were presented at the American Academy of Neurology (AAN) 69th Annual Meeting in April, 2017 (Kuntz, 2017; Mercuri, 2017; De Vivo, 2017).
- The final results of the ENDEAR and CHERISH trials are consistent with the interim findings with evidence sufficient to determine that treatment with nusinersen results in a meaningful improvement in the net health outcome, including overall survival, event-free survival, functional outcomes (motor milestones) with a favorable safety profile.

Type II and III SMA

The evidence for Type II or III SMA who receive Spinraza (nusinersen), includes:

4 single arm studies

- Efficacy from single arm studies is difficult to interpret because these trials used a wide range of Spinraza (nusinersen) doses, included both type II and III and lacked a control arm.

1 double-blind RCT (CHERISH)

- Results of the confirmatory phase III CHERISH trial were presented at the annual American Academy of Neurology (AAN) meeting in April 2017.
- CHERISH: Phase III, randomized, double-blind, sham-controlled study of 126 patients (84 on nusinersen, 42 controls) with type 2 SMA; 88% had three copies of the SMN2 gene [range: two to four), and onset of clinical signs and symptoms consistent with SMA at > age six months.

- **The study has shown that nusinersen is effective in the later-onset SMA children similarly to that observed in early-onset SMA children.**
- Nusinersen-treated children demonstrated significant and clinically meaningful improvements in motor function vs. sham based on HFMSE and WHO motor development milestones measures.
    - In the data, it was noted that in more than 57% of the treated patients, Hammersmith Functional Motor Scale–Expanded (HFMSE) scores improved by 3 or more points at month 15, compared to about 20% of the controls.
- The trial reported a "favorable safety profile" with no withdrawals due to adverse events.
    - Most frequent AEs were back pain, headache, and vomiting, and occurred at a ≥5% higher frequency in the nusinersen group 72 hours following drug administration, likely related to the lumbar puncture procedure.
    - No evidence of adverse effects on platelet counts, renal function, or hepatic enzymes.
- Patients from CHERISH transitioned to the SHINE open label extension.

The FDA approved indication is for all SMA patients; however, there is limited published data and evidence of efficacy on the following patients, including: older children, adults, SMA Type 0 and IV, and patients requiring with advanced disease or requiring permanent ventilation.

No studies evaluating nusinersen enrolled patients older than 18 years of age and the current FDA approved indication for nusinersen is based principally on the results of a planned interim analysis that was conducted in a subset of patients enrolled in a multicenter, double-blind, sham procedure-controlled phase 3 study (ENDEAR)

- Published phase 3 trials, ENDEAR and CHERISH:
    - 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
- Results of additional open-label uncontrolled trials in symptomatic patients **30 days to 15 years of age** and presymptomatic patients 8 to 42 days of age provide supporting evidence for the use of nusinersen in other stages of spinal muscular atrophy, including later-onset disease [Finkel et al. 2017; Chiriboga et al. 2016].

The FDA approved indication does not limit the use of Spinraza (nusinersen) to any of the SMA types; however, the efficacy and safety data was only conducted in patients with symptomatic SMA and in pre-symptomatic patients with, or likely to, develop Type 1, 2 or 3 SMA and **there are no data on patients with Type 4 included in the FDA approved package insert.**

SMA Type 0 and IV

There is insufficient evidence to support safety and efficacy of nusinersen in SMA Type 0 or 4 at this time. There are currently no published trials or interim studies to support the safety and efficacy of nusinersen in SMA Type 0 and 4.

SMA Patients requiring Permanent Ventilation

Clinical studies have demonstrated that Spinraza (nusinersen) 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. Therefore, due to the lack of evidence establishing safety and efficacy in these individuals, Spinraza (nusinersen) is considered investigational in members who already require permanent ventilation.

Anti-drug antibodies (ADAs)
Nusinersen was determined to illicit an immunogenic response in 126 of the 173 individuals exposed to the drug in clinical trials who had baseline plasma samples evaluated for anti-drug antibodies (ADAs). The labeling states: **There is insufficient data to evaluate an effect of anti-drug antibodies on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.** (Biogen Inc., 2017)

The clinical effects of ADAs after clinical trials and data are submitted to the FDA and published will be evaluated and updated in this policy accordingly.

There is insufficient evidence to establish definitive patient selection criteria for nusinersen treatment of SMA (Hayes, 2020).

- One fair-quality randomized sham-controlled study evaluated whether disease duration had an impact on nusinersen efficacy in infants with type 1 SMA. The probability of overall event-free survival was greater among infants with a shorter duration of disease (symptoms for ≤ 13.1 weeks) who were treated with nusinersen (77%) compared with sham (33%) (HR, 0.24; 95% CI, 0.10-0.58) compared with those with symptoms for > 13.1 weeks (HR, 0.84; 95% CI, 0.43-1.67) (Finkel et al., 2017).
- One prospective pretest/posttest study assessed whether age or the number of copies of SMN-2 had an impact on efficacy of nusinersen in infants and children with SMA type 1 who were treated under an expanded access program. The mean improvement in CHOP-INTEND score was significantly greater in patients who began treatment under the age of 7 months (14.4 points) versus those over the age of 7 months (7 points) (P=0.0006), suggesting that age at treatment initiation was a determinant in efficacy of treatment (Pechmann et al., 2018a). Analysis of the number of copies of SMN-2 did not identify any difference in effect on the CHOP-INTEND score (≤ 2 SMN-2 copies 8.1 ± 7; ≥ 3 SMN-2 copies 8.2 ± 5.3; P=NR).
- One study conducted in patients with type 2 or 3 SMA found that among patients in the 9 mg group, improvement in HFMSE score of ≥ 3 points was observed to a similar extent in patients with either type 2 (71%) or type 3 (66%) SMA (Chiriboga et al., 2016).

FDA INDICATIONS

Spinal Muscular Atrophy: Treatment of spinal muscular atrophy (SMA)[†]
[†]*Orphan drug designation: Spinal muscular atrophy*

Available as: 12 mg/5 mL solution for injection; single-dose vial. Supplied as a solution for intrathecal administration

FDA Approved: December 2016

- Granted accelerated FDA approval on December 23, 2016 for the treatment of SMA. The approval was granted under Priority Review; the FDA also granted Orphan Drug Designation to Spinraza for the treatment of patients with SMA.
- FDA approval under priority review was received within three months of regulatory filing

Black Box Warnings/REMS: *None*

Warnings/Precautions

- Hematologic effects: Coagulation abnormalities and thrombocytopenia (including acute severe thrombocytopenia), have been observed with some antisense oligonucleotides; increased risk of bleeding complications may occur. Perform a platelet count and coagulation testing at baseline, prior to each dose and as clinically needed.
- Renal toxicity, including potentially fatal glomerulonephritis, has been observed with some antisense oligonucleotides. Conduct quantitative spot urine protein testing (preferably using first morning urine) at baseline and prior to each dose. For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation.

CLASSIFICATION: Musculoskeletal Agents; Antisense Oligonucleotide[§]

[§]*Antisense oligonucleotides 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)*

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Spinraza (nusinersen) may be authorized for initial therapy for members who meet **ALL** the following criteria **[ALL]**

1. Prescriber specialty [ONE]

❒ Prescribed by, or in consultation with, a board-certified pediatric neurologist or neurologist with experience in the diagnosis and management of spinal muscular atrophy (SMA)
- *The FDA's risk assessment review cites Hache et al, as the author describes that prescribers of nusinersen are expected to be pediatric neurologists or other members of the multidisciplinary clinical team (Hache M, et al. 2016)*

2. Diagnosis/Indication [ALL]

Documentation of diagnosis required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis. Submit all relevant clinical documentation at the time of the request.

❒ Clinical diagnosis of ONE (1) of the following types of SMA [ONE]
- ❍ SMA Type I
- ❍ SMA Type II
- ❍ SMA Type III

NOTE: There is insufficient evidence to support safety and efficacy of nusinersen in SMA Type 0 or 4.

❒ Genetic testing confirms the presence of ONE (1) of the following: [ONE]
- ❍ Homozygous deletions of SMN1 gene (e.g., homozygous deletion of exon 7 at locus 5q13)
- ❍ Homozygous mutation in the SMN1 gene (e.g., biallelic mutations of exon 7)
- ❍ Compound heterozygous mutation in the SMN1 gene [e.g., deletion of SMN1 exon 7 (allele 1) and mutation of SMN1 (allele 2)]

❒ At least 2 copies of the SMN2 gene

Informational Note

- *SMA Type I: The ENDEAR study recruited patients up to 7 months of age with infantile-onset SMA with documented 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote, and only two copies of the SMN2 gene. These characteristics make this group of patients likely to develop SMA Type I.*
- *Genetic testing is the standard diagnostic test for SMA, which is supported in the 2007 Consensus Statement for Standard of Care in Spinal Muscular Atrophy. Since the majority of patients (95-98%)[NORD 2018] have deletions in SMN1, the authors describe that the SMN gene deletion test should be the first diagnostic test ordered when SMA is suspected (Wang et al. 2007).*
- *The survival motor neuron 2 (SMN2) gene produces a small amount of functional SMN protein. The number of copies of the SMN2 gene is variable in humans. In SMA, a higher number of SMN2 copies is correlated with less severe disease. It is unknown whether patients with less than 2 copies would make sufficient SMN protein to mitigate the symptoms of SMA as the efficacy of this agent has not been demonstrated in patients with less than 2 copies of SMN 2 genes.*

❒ Member is **not** dependent on either of the following: [ANY]

- ❍ Invasive ventilation (for not more than 16 hours per day) or tracheostomy; or
- ❍ Use of non-invasive ventilation beyond naps and nighttime sleep, or Non-invasive ventilation for at least 12 hours per day

NOTE: Spinraza has not been studied in patients who already require permanent ventilation in any sub-type of SMA. **Therefore, Spinraza is considered investigational in patients who already require permanent ventilation due to the lack of evidence demonstrating Spinraza will be safe and effective in those patients.**

Informational Note:

- *No patients in the ENDEAR trial required permanent ventilation at baseline, and as a co-primary efficacy end point in the trial, 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.*
- *Less robust data suggest that older children and adults may also benefit (Hagenacker T, et al. 2020). However, children or adults who are ventilator-dependent, need enteral feeds, or have severe contractures or scoliosis may be too debilitated to derive benefit from nusinersen.*

3. Age/Gender/Restrictions [ALL]

❒ 15 years of age or younger at initiation of treatment

Informational Note:

- *For most infants with SMA, treatment with nusinersen is recommended (Grade 1B).*
- *For children up to 12 years of age with moderate symptoms of SMA, similar to those enrolled in the CHERISH trial, treatment with nusinersen is suggested (Grade 2C).*
- *Limited observational data suggest that older children, adults, and patients with advanced SME may benefit from nusinersen. UpToDate 2020*
- *There is insufficient evidence to support safety and efficacy of nusinersen in SMA Type 0 or 4. No studies evaluating nusinersen enrolled patients older than 18 years of age.*
- *Published phase 3 trials, ENDEAR and CHERISH:*
  - *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*

❒ Confirmation of member's enrollment status in clinical trials for Spinraza (nusinersen)

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

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

❒ Baseline motor function assessment using at least **ONE (1)** of the following assessment tools† appropriate for participant age and motor function (to establish baseline motor ability prior to therapy initiation): [ONE]

†Three measures have been developed and validated specifically for SMA populations

- ❍ †CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders: Appropriate for infants with SMA Type I and children with an infant's repertoire of motor skills
- ❍ †HFMS: Hammersmith Functional Motor Scale: For patients with SMA types 2 or 3
- ❍ †HFMSE: Hammersmith Functional Motor Scale Expanded: Appropriate for later-onset SMA in persons over 24 months; ambulatory patients with SMA types 2 or 3
- ❍ Hammersmith Infant Neurologic Exam Part 2 (HINE-2): Appropriate for infants ages from 2 months to 2 years of age (not specifically designed for those with SMA type I, it has been used in several SMA clinical trials)
- ❍ 6-minute walk test (6MWT): Ambulatory patients with later-onset (Type 2 or Type 3) SMA
- ❍ Revised Upper Limb Module (RULM) score: Non-ambulatory patients over 30 months

Refer to APPENDIX 2: Assessment tools for motor development

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

  NOTE: A platelet count, coagulation laboratory testing, and quantitative spot urine protein testing are recommended at baseline and prior to each dose of Spinraza and as clinically needed-- due to the risk of coagulation abnormalities, thrombocytopenia, and renal toxicity.

- ❒ Prescriber agrees to submit a clinical progress report including treatment outcomes on the member every 6 months following initial dosing is required for continuation of treatment requests

Informational Note

- *Thrombocytopenia and coagulation abnormalities have been reported with some antisense oligonucleotides. Platelet counts are required at baseline, prior to each dose, and as clinically needed throughout therapy. In a clinical trial, no patients had a platelet count less than 50,000 cells/mL or a sustained low platelet count despite continued drug exposure.*
- *Renal toxicity, including potentially fatal glomerulonephritis, has been reported with some antisense oligonucleotides. Higher rates of urine protein elevation occurred in treated patients (33%) vs. controls (20%) in clinical trials. In general, renal toxicity has been observed after administration of some antisense oligonucleotides.*
- *Quantitative spot urine protein testing (preferably using a first morning urine specimen) is required at baseline and prior to each dose. If urinary protein concentration is 0.2 or higher, the test should be repeated, and further evaluation considered.*

5. Contraindications*/Exclusions/Discontinuations

**There are no contraindications listed in the manufacturer's labeling and the manufacturer states that no drug interaction studies have been conducted to date.*

Authorization will not be granted if ANY of the following conditions apply [ANY]

Exclusions

- ❒ Non-FDA approved indications
- ❒ 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)
- ❒ Respiratory insufficiency: Member has not received a tracheostomy or become ventilator dependent
- ❒ 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: [ANY]
  - ❍ Untreated or inadequately treated active infection, or presence of infected skin at the target puncture site
  - ❍ History of brain or spinal cord disease or abnormalities, tumors, severe contractures, or severe scoliosis
  - ❍ Implanted shunt for the drainage of cerebrospinal fluid (CSF) or an implanted central nervous system (CNS) catheter
  - ❍ History of bacterial meningitis
  - ❍ 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
  - ❍ Presence of unequal pressures between the infratentorial and supratentorial compartments (Shalmovitz and Shah, 2017)
  - ❍ Coagulopathy, brain abscess, or increased intracranial pressure (Relative contraindications for lumbar puncture)
- ❒ Concomitant or previous participation in clinical trials for SMA treatment, SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy study
- ❒ Concurrent therapy with nusinersen OR previously received gene replacement therapy for the treatment of SMA [e.g. Zolgensma (onasemnogene abeparvovec)]

Discontinuations

- ❑ Intolerable adverse effects or drug toxicity
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

REAUTHORIZATION /CONTINUATION OF THERAPY

Spinraza (nusinersen) may be authorized for continuation of therapy if meet **ALL** the following criteria are met: **[ALL]**

1. Initial Coverage Criteria [ALL]

- ❑ Subsequent authorizations will require the Member to have an office visit and re-assessment for this condition annually to determine if continuation of treatment with requested medication is medically necessary. Chart notes or consultation notes (if applicable) must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Compliance [ALL]

- ❑ 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 [MEDICAL DIRECTOR REVIEW]

  NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence has been demonstrated during the course of authorization [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY]

3. Labs/Reports/Documentation required [ALL]

Spinraza (nusinersen) therapy may be authorized when therapy has demonstrated efficacy as evidenced by disease stabilization or improvement: [ALL]

- ❒ At least ONE (1) positive clinical response based on provider's assessment (evaluated within 30 days of request) documenting significant improvement or maintenance of function from pretreatment baseline status [ONE]
  - ❍ CHOP-INTEND: At least 4-point increase from pretreatment baseline
  - ❍ HFMSE: At least 3-point increase from pretreatment baseline
  - ❍ HINE: 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
  - ❍ 6-minute Walk Test (6MWT): Increase of 30 meters if ambulatory
  - ❍ Upper Limb Module (ULM) score: At least 2-point increase from pretreatment baseline
  - ❍ Achievement of new motor milestone from pretreatment baseline that is otherwise not expected, OR Improvement in more categories of motor milestones than worsening
  - ❍ Member remains permanently ventilator-free

  NOTE: 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

- ❒ Clinical progress report including treatment outcomes since last dosage/administration of therapy

- ❒ Submission of the following labs (dated within the past 30 days of request): [ALL]
  - ❍ Quantitative spot urine protein testing
  - ❍ Platelet count
  - ❍ Prothrombin time (activated partial thromboplastin time)

  NOTE: A platelet count, coagulation laboratory testing, and quantitative spot urine protein testing are recommended at baseline and prior to each dose of Spinraza and as clinically needed-- due to the risk of coagulation abnormalities, thrombocytopenia, and renal toxicity.

4. Contraindications*/Exclusions/Discontinuations

**There are no contraindications listed in the manufacturer's labeling and the manufacturer states that no drug interaction studies have been conducted to date.*

Exclusions

- ❒ Non-FDA approved indications
- ❒ 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)
- ❒ Respiratory insufficiency: Member has not received a tracheostomy or become ventilator dependent
- ❒ 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: [ANY]
  - ❍ Untreated or inadequately treated active infection, or presence of infected skin at the target puncture site
  - ❍ History of brain or spinal cord disease or abnormalities, tumors, severe contractures, or severe scoliosis
  - ❍ Implanted shunt for the drainage of cerebrospinal fluid (CSF) or an implanted central nervous system (CNS) catheter
  - ❍ History of bacterial meningitis
  - ❍ 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
  - ❍ Presence of unequal pressures between the infratentorial and supratentorial compartments (Shalmovitz and Shah, 2017)
  - ❍ Coagulopathy, brain abscess, or increased intracranial pressure (Relative contraindications for lumbar puncture)
- ❒ Concomitant or previous participation in clinical trials for SMA treatment, SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy study
- ❒ Concurrent therapy with nusinersen OR previously received gene replacement therapy for the treatment of SMA [e.g. Zolgensma (onasemnogene abeparvovec))]

Discontinuations

- ❑ Intolerable adverse effects or drug toxicity
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms

5. **Labs/Reports/Documentation required [ALL]**
   All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included.

   NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. **Recommended Dosage [ALL]**
   - ❒ 12 mg (5 mL) intrathecally per administration
   - ❒ Initial dosing: Initiate treatment with 4 loading doses; the first three loading doses should be administered at 14-day intervals; the 4th loading dose should be administered 30 days after the 3rd dose
   - ❒ Maintenance dosing: A maintenance dose should be administered once every 4 months thereafter. If a maintenance dose is delayed or missed, administer Spinraza as soon as possible and continue dosing once every 4 months.

2. **Authorization Limit [ALL]**
   - ❒ Quantity limit: [ALL]
     - ❍ Maximum dose: 12mg per dose
     - ❍ Loading: Five 5mL (12mg/5mL) vials for the first 6 months [to allow for 4 loading doses (Day 0, 14, 28, 58) and 1 maintenance dose after 4 months
     - ❍ Maintenance: 12 mg (1 vial) every 4 months
     - ❍ Annual quantity limit: Three 5mL (12mg/5mL) vials for the subsequent 12 months

   - ❒ Duration authorization: [ALL]
     - ❍ Initial: 6 months
     - ❍ Continuation: Re-authorization is required every **6 months** to determine effectiveness of therapy and continued need based on documented positive clinical response. Subsequent renewals will be authorized upon verification of marked clinical improvement demonstrated by objective improvement in these selected markers. *Refer to 'Continuation of Therapy' section.*

3. **Route of Administration [ALL]**
   - ❒ Spinraza (nusinersen) is to be administered by, or under the guidance of, healthcare professionals experienced in performing lumbar puncture

   - ❒ Refer to Specialty Medication Administration Site of Care Policy P&P: MHI Pharm 11

COVERAGE EXCLUSIONS

This policy addresses the coverage of Spinraza (nusinersen) for the treatment of **spinal muscular atrophy (SMA)**. The intent of this MCP is to ensure appropriate selection of patients for therapy based on current available evidence, product labeling, clinical guidelines, and clinical studies.

All other uses of Spinraza (nusinersen) that are not an FDA-approved indication AND not included in the 'Coverage Criteria' section of this policy is considered not medically necessary. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

Off Label Uses: AHFS Drug Information 2020 Edition does not support any off-label uses of Nusinersen (Spinraza)

- ❒ **SMA Type 0 or 4:** There is insufficient evidence to support safety and efficacy of nusinersen in SMA Type 0 or 4
  - The safety and effectiveness of nusinersen (Spinraza) in conditions other than SMA types 1, 2, or 3 have not been established. There is insufficient evidence to establish the efficacy of nusinersen for the treatment of very late onset SMA (SMA type 4 or adult onset). Trials of nusinersen included patients up to 12 years of age, but not older.
  - SMA type IV is very rare. It usually surfaces in adulthood, and it leads to mild motor impairment. While symptoms can begin as early as age 18, they usually begin after age 35.
- ❒ **15 years of age and older:** No studies evaluating nusinersen enrolled patients older than 18 years of age.
  - For most infants with SMA, treatment with nusinersen is recommended (Grade 1B). For children up to 12 years of age with moderate symptoms of SMA, similar to those enrolled in the CHERISH trial, treatment with nusinersen is suggested (Grade 2C). UpToDate 2020
  - There are limited observational data that suggest that older children and adults may benefit from nusinersen treatment. UpToDate 2020
  - Published phase 3 trials, ENDEAR and CHERISH:
    - 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
  - The results of the controlled trial in infantile-onset SMA patients were supported by open-label uncontrolled trials conducted in symptomatic SMA patients who ranged in age from 30 days to 15 years at the time of first dose, and in pre-symptomatic patients, who ranged in age from 8 days to 42 days at the time of first dose (Biogen, 2016). The patients in these studies had or were likely to develop Type 1, 2, or 3 SMA. Some patients achieved milestones such as ability to sit unassisted, stand, or walk when they would otherwise be unexpected to do so, maintained milestones at ages when they would be expected to be lost, and survived to ages unexpected considering the number of SMN2 gene copies of patients enrolled in the studies.
- ❒ **SMA Type I, II, and III SMA with Permanent Ventilation**
  - No patients in the ENDEAR trial required permanent ventilation at baseline, and as a co-primary efficacy end point in the trial, 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.
- ❒ Concomitant or previous participation in clinical trials for SMA treatment, SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy study
- ❒ Concurrent therapy with nusinersen OR previously received gene replacement therapy for the treatment of SMA [e.g. Zolgensma (onasemnogene abeparvovec))]

PUBLISHED PHASE 3 TRIALS

The current indication for nusinersen is based principally on the results of a planned interim analysis that was conducted in a subset of patients enrolled in a double-blind, sham procedure-controlled phase 3 study (ENDEAR).

ENDEAR: Infantile-onset SMA (7 months of age or younger)

Phase 3 (n=121; 13 months); To Assess the Efficacy and Safety of Nusinersen in patients with **infantile-onset** SMA

A 13-month, international, double-blind, randomized trial assessing nusinersen versus a sham procedure. A total of 122 patients were randomized into the treatment groups (Kuntz, 2017)

One phase 3 randomized, double-blinded, sham-controlled trial (ENDEAR) evaluated nusinersen (Spinraza) vs. sham injection in SMA1 in children started at less than 7 months of age.

- All subjects had onset of SMA symptoms prior to the age of 6 months and a diagnosis genetically confirmed.
- Motor milestones were evaluated based on the Hammersmith Infant Neurological Exam (HINE) categories (in the modified section 2).
- "Motor milestone responder" was defined as more categories of improvement than worsening, based on the modified section 2 of the HINE.
- The proportion of subjects who were motor milestone responders was significantly higher with nusinersen (Spinraza) than placebo, based on a preplanned interim analysis. (n=82).

INTERIM EFFICACY ANALYSIS of the ENDEAR trial

The interim analysis was conducted based on patients who had received at least 183 days of treatment, withdrawn from the study, or died, and included a total of 82 patients (56% female, 87% white, and 98% with 2 copies of the SMN2 gene). Based on the positive results of the interim analysis, the ENDEAR study was terminated early and all patients were transitioned to active treatment with nusinersen.

- Among the 82 patients who were included in the interim analysis, **40% achieved a motor milestone response compared with none of the patients in the control group.**
- Motor function also was assessed by the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) as a secondary end point in this study; although the test was not statistically controlled for multiple comparisons, an improvement in CHOP-INTEND score (defined as an increase from baseline of at least 4 points) was achieved in 63% of patients in the nusinersen group compared with 3% of patients in the control group, and a worsening of the CHOP-INTEND score (defined as a decrease from baseline of at least 4 points) occurred in 4 and 40% of patients in the respective treatment groups.
    - **Patients were invited to enroll in the open-label extension study SHINE (ClinicalTrials.gov number, NCT02594124).**

IN THE FINAL ANALYSIS of the ENDEAR trial

- Improvement in motor milestones was noted in 37 of 73 (51 percent) infants treated with nusinersen, versus 0 of 37 (0 percent) of infants who received the sham procedure (37 of 73 infants [51%] vs. 0 of 37 [0%]) [Finkel RS, et al. 2017].

- In the nusinersen treatment group, motor milestones achieved included head control (22 percent), rolling over (10 percent), sitting independently (8 percent), and standing (1 percent). In the sham procedure group, no infants achieved motor milestones.
- The likelihood of **event-free survival was higher in the nusinersen group** than in the control group. The proportion of **infants who died or received permanent assisted ventilation was lower in the nusinersen group** compared with the sham group (39 versus 68 percent, hazard ratio 0.53, 95% CI 0.32-0.89).
- The likelihood of **overall survival was higher in the nusinersen group than in the control group** (hazard ratio for death, 0.37; P = 0.004), and **infants with a shorter disease duration** at screening were more likely than those with a longer disease duration to benefit from nusinersen.

Reference: ClinicalTrials.gov Identifier: NCT 02193074

CHERISH: Later-onset SMA; Older Children with SMA (2 to 12 years of age)
Phase 3 (n=126, 15 months)

To assess the efficacy and safety of Nusinersen in children with later-onset SMA

One phase 3 randomized, double-blinded, sham-controlled trial (CHERISH) evaluated nusinersen vs. sham injection in 126 pediatric patients (84 on nusinersen, 42 controls) in later-onset SMA (types 2 and 3) from 2-12 years old at screening with Type II SMA. (Mercuri, 2017)

- All subjects had onset of SMA symptoms at > 6 months of age, were between the age of 2 and 12 years of age at the time of screening for the trial, and the diagnosis of SMA was genetically confirmed. All subjects could sit independently, but never had the ability to walk independently.
- Motor function was evaluated based on the Hammersmith functional motor scale expanded (HFMSE) score. A change from baseline of > 3 points was considered a responder.
- Subjects in the nusinersen (Spinraza) arm had a significantly higher change in HFMSE versus those in the placebo arm. (+5.9 points, placebo-subtracted). Key secondary endpoints that were statistically higher with nusinersen vs. placebo included percent of HFMSE responders (56.8% vs. 26.3%; p=0.006) and number of new motor milestones (+0.2 vs. -0.2; p<0.0001). However, more meaningful health outcomes of standing along and walking without assistance were not different between treatment arms, though secondary outcomes and not powered for statistical significance.

Interim Analysis A pre-specified interim analysis was conducted when all patients had been enrolled for at least 6 months and at least 39 children had completed the 15-month assessment. A multiple-imputation method to account for missing data was used for those patients that did not have 15-month results at the interim analysis.

- At the interim analysis, there was a significant improvement favoring the treatment group (least squares mean difference in change, 5.9 points; 95% CI, 3.7 to 8.1; P<0.001).
- Patients transitioned to the **SHINE** open-label extension study (ClinicalTrials.gov number, NCT02594124).

Primary Endpoints

- Least-squares mean change from baseline in the total HFMSE score at month 15. HFMSE assessments performed at 3, 6, 9, 12, and 15 months; authors cite that a change in the HFMSE score of at least 3 points is considered to be clinically significant.

Secondary Endpoints

- Percentage of patients who had an increase from baseline to month 15 in the HFMSE score of at least 3 points
- Percentage of patients who achieved at least one new World Health Organization motor milestone (out of a total of six milestones), (3) the change from baseline in the Revised Upper Limb Module (RULM) score (which ranges from 0 to 37, with higher scores indicating better function
- Proportion of children who had achieved the ability to stand alone or walk with assistance
- Change from baseline to month 15 in the HFMSE score according to age and disease duration

Results

- Nusinersen-treated children demonstrated significant and clinically meaningful improvements in motor function vs. sham based on HFMSE and WHO motor development milestones measures.
- In the final analysis, a significantly more positive difference from baseline in the HFMSE score was in favor of nusinersen (least-squares mean difference in HFMSE change, 4.9 points; 95% CI, 3.1 to 6.7).
- Regarding secondary endpoints, although there were significantly more patients in the treatment group with an increase in the HFMSE score of at least 3 points (57% vs. 26%, P<0.001), there was no significant difference in the number of patients who achieved at least one World Health Organization motor milestone compared to the controlled group (Mercuri E, et al. 2018)
- The overall incidence of adverse events was similar in the nusinersen group and the control group.

Reference: ClinicalTrials.gov Identifier: NCT 02292537

ONGOING CLINICAL TRIALS

SHINE (ClinicalTrials.gov Identifier: NCT 02594124)

An Open-Label Extension Study for Patients with SMA who previously participated in Investigational Studies of Nusinersen (ENDEAR or CHERISH participants)

- Estimated Enrollment: 274
- Study Start Date: November 2015
- Estimated Study Completion Date: February 2020

Two Phase II studies: EMBRACE and NURTURE

EMBRACE (ClinicalTrials.gov Identifier: 02462759)

The EMBRACE study is a randomized, double-blind, sham-procedure controlled study of safety, tolerability, and efficacy of nusinersen in persons with SMA who are not eligible to participate in either the ENDEAR or CHERISH study.

- **SMA type 1**
- Phase 2, double-blind, randomized, sham-procedure controlled clinical study evaluating the safety and exploratory efficacy of the investigational drug, nusinersen, in patients with infantile or childhood-onset SMA over a 14 month period (n= 20)
- The EMBRACE study is a two-part study for SMA patients not eligible for the ENDEAR or CHERISH studies with a randomized, sham-controlled part followed by an open-label extension part:
  - Part 1 is a randomized, double-blind, sham-controlled study
  - Part 2 is an open-label extension study
- Interim analysis Data presented at the International Annual Congress of the World Muscle Society October 2017 showed a larger portion of infants and children treated with Spinraza had responses in motor

function per the HINE scale than untreated patients. The data also supported dosing Spinraza using 4 loading doses within the first two months followed by subsequent dosing every four months.

NURTURE (ClinicalTrials.gov Identifier: NCT02386553)

Presymptomatic Infants with SMA A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants with Genetically Diagnosed and Presymptomatic SMA

- **Genetic predisposition for SMA**
- Phase 2, open-label, multicenter, multinational, single-arm study of 20 infants less than 6 weeks old with genetically diagnosed SMA, pre-symptomatic at treatment initiation, and two (n=13) or three (n=7) copies of SMN2
- Primary endpoint: Event survival (time to death or respiratory intervention) and HINE-2 motor milestone achievements.

Interim results

- Event-free survival was 100% at a median 317.5 days (range 2.0 to 524.0 days)
- Infants achieved motor milestones and growth parameters consistent with normal development, but unlikely to be achieved by infants with SMA Type I or II.
- Most infants achieved motor milestone and growth parameter gains generally consistent with normal development, such as head control, independent sitting, standing, and walking independently.
- 80% patients experienced adverse events, but none involved specific safety concerns or caused withdrawals from the study.

Systematic Reviews/Meta-analyses

No systematic reviews or meta-analyses regarding nusinersen treatment of SMA were identified.

HAYES

A Precision Therapy Assessment addressing 'Nusinersen (Spinraza; Biogen) for Spinal Muscular Atrophy' (published Jun 7, 2018 with annual reviews) concluded that there is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management and assigned **a D2 rating "Insufficient evidence"** for the use of nusinersen in the following types of SMA.

- Infants with SMA type 1
- Infants and children with SMA type 2 or 3
- Adults with any subtype of SMA: No eligible studies were identified.

A D2 Rating reflects a very-low-quality body of evidence that does not allow for conclusions to be drawn. Substantial uncertainty exists due to the shortage of comparative studies, limited number of studies, lack of clear and clinically significant improvement, lack of comparable patient populations, and lack of adequate follow-up.

CLINICAL PRACTICE GUIDELINES

American Academy of Neurology (AAN)/American Academy of Pediatrics (AAP)
The American Academy of Neurology published systematic review of the evidence for the use of nusinersen in SMA (2018) with the endorsement of the AAP.

The systematic review resulted in the following: Four published clinical trials were identified, 3 of which were rated above Class IV.

- There is Class III evidence that 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.
- There is Class I evidence that in term infants 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.
- There is Class I evidence that 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.

The authors concluded that the evidence of efficacy is currently highest for treatment of infantile- and childhood-onset SMA in the early and middle symptomatic phases. Although approved indications for nusinersen use in North America and Europe are broad, payer coverage for populations outside those in clinical trials remain variable. Evidence, availability, cost, and patient preferences all influence decision-making regarding nusinersen use.

2018 Cure SMA Working Group
Cure SMA Working Group (2018) treatment algorithm, the working group stresses the need for early intervention through newborn screening to maximize the benefit of treatment. The group recommends the development of dependable and validated screening techniques to enable treatment of pre-symptomatic patients who may be more responsive to treatment than those already experiencing symptoms.

- For patients with SMA Types II or III with three or fewer copies of the SMN2 gene, the group recommends immediate treatment with a disease modifying therapy and referral to both a neuromuscular specialist and a geneticist; for those with only one copy of SMN2 who are symptomatic at birth, the group states that the attending physician should determine whether the patient and family would benefit from treatment. Lastly, patients with four copies of SMN2 should be screened periodically for symptoms and referred to a geneticist to determine the exact number of SMN2 copies, but the working group recommends against immediate treatment with a disease modifying therapy. (Glascock J et al 2018)

Cure SMA Working Group (2019) reassessed the treatment algorithm for newborns with SMA identified through newborn screening based upon new experience and therapeutic options. The working group has updated or revised their position for the following recommendation:

- Immediate treatment for infants diagnosed with SMA via newborn screening with four copies of SMN2
- Wait to treat for infants with five copies of SMN2 and unanimously voted to uphold the recommendation of watchful waiting
- The working group acknowledged that current laboratory assays designed to detect SMN2 copy number often have difficulty distinguishing high copy numbers of SMN2 and that many laboratories report results as four or more SMN2 copies, being unable to give an exact number. Recognizing this fact, the working group encouraged follow-up with a laboratory able to distinguish exact SMN2 copy number. (Glascock J et al 2019)

DEFINITIONS

N/A

APPENDIX

APPENDIX 1: Classification of Spinal Muscular Atrophy

Disease phenotypes are classified according to a scheme developed at the 1991 International Consortium on Spinal Muscular Atrophy sponsored by the Muscular Dystrophy Association; these phenotypes were modified into six subtypes on the basis of age of onset, inheritance pattern, and maximum motor function achieved (Kolb, 2015; Munsat, 1991):

SMA Type 0 Prenatal forms of SMA

- **The most severe form of SMA, symptoms can often be seen in the later stages of pregnancy.** Fetal movements are less than expected and, after birth, the infant will have little ability to move and may not be able to breathe and swallow independently.
- Death occurs before the age of 6 months
- No milestones achieved
- Severe weakness, joint contractures, early respiratory failure

SMA Type 1 Acute infantile SMA; Infantile SMA, Progressive muscular atrophy of infancy; Werdnig-Hoffman disease

- **The most common type of SMA** (accounts for approximately 60% of all patients with SMA)
- **Onset within 6 months of birth** and symptoms progress rapidly, and **most infants die before 1 year of age from respiratory failure**
- Infant with SMA type I face many physical challenges, including muscle weakness and trouble breathing, coughing, and swallowing. They may need breathing assistance or a feeding tube.
- Characterized by inability to sit unsupported; these babies do not reach the developmental milestone of sitting. Affected infants are developmentally delayed; most are unable to support their head or sit unassisted
- Breathing and swallowing problems that may lead to choking or gagging
- **Two copies of the SMN2 gene** are usually present

SMA Type II Chronic infantile form; Childhood SMA; Chronic SMA; Dubowitz disease

- **Onset within 6 to 18 months** with a less severe progression
- Typically, a child can sit independently if positioned, but is unable to walk. Many patients will ultimately lose the ability to sit
- At **least three SMN2 genes** are usually present

SMA Type III Chronic juvenile; Juvenile SMA: Kugelberg-Welander disease;

- May be classified further as type 3a (18 months to 3 years of age) and type 3b (> 3 years old)
- **Usually diagnosed after 18 months of age, but before three years of age. However, SMA type III can be diagnosed as late as the teenage years.**
- Individuals affected by SMA type III are initially able to walk but have increasingly limited mobility as they grow and eventually, many need to use a wheelchair.
- Characterized by loss of ability to walk during childhood (or later during adolescence or adulthood), usually presenting as progressive proximal weakness but without respiratory muscle weakness
- Usually **four to eight SMN2 genes** are present

SMA Type IV (Adult-onset SMA)

- Rare and is the mildest form of SMA
- **Usually surfaces in adulthood: as early as age 18 but usually presents in the third decade of life**
- Usually surfaces in adulthood, and it leads to mild motor impairment.
- Patients remain ambulatory but may have hip and shoulder girdle weakness mimicking a mild limb-girdle muscular dystrophy.

APPENDIX 2: ASSESSMENT TOOLS FOR MOTOR DEVELOPMENT

ASSESSMENT TOOLS FOR MOTOR DEVELOPMENT	
SMA Outcome Measures	**Description**
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 *References:* *Glanzman AM, Mazzone E, Main M, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. Neuromuscular disorders: NMD. 2010;20(3):155-161.* *De Sanctis R, Pane M, Coratti G, et al. Clinical phenotypes and trajectories of disease progression in type 1 spinal muscular atrophy. Neuromuscular disorders: NMD. 2018;28(1):24-28.*
HINE-2 Hammersmith Infant Neurological Exam Section 2	• Clinician-administered tool to evaluate motor function in children age 2 to 24 mo • Measures achievement of 26 motor milestones in 8 areas (i.e., walking, standing, crawling, rolling, kicking, grasping, sitting, and head control) • 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 are able to achieve each milestone. This scale been used for SMA type 1 patients. *References:* *Bishop KM, Montes J, Finkel RS. Motor milestone assessment of infants with spinal muscular atrophy using the Hammersmith infant neurological Exam-Part 2: Experience from a nusinersen clinical study. Muscle & nerve. 2018;57(1):142-146.* *Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. The New England journal of medicine. 2017;377(18):1723-1732.*
HFMSE Hammersmith Functional Motor Scale-Expanded Test	• Clinician-administered tool designed to measure motor function in children with with later-onset SMA Type 2 and 3, including non-ambulatory and ambulatory patients • Assessment includes 33 items total

	• Total scores range from 0 to 66 points; higher scores indicate better function • 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 degree of motor ability • 3-point change is considered clinically significant • Assessment was employed in the phase 3 CHERISH nusinersen study for late-onset SMA. Furthermore, authors of the CHERISH study note, "A change in the HFMSE score of at least 3 points is considered to be clinically meaningful." *References:* • *O'Hagen JM, Glanzman AM, McDermott MP, et al. An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. Neuromuscular disorders: NMD. 2007;17(9-10):693-697.* • *Center for Drug Evaluation and Research. Application Number 209531Orig1s000: Summary Review. U.S. Food and Drug Administration. Silver Spring, MD https://www.accessdata.fda.gov/drugsatfda docs/nda/2016/209531Orig1s000TOC.cfm* • *Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. The New England journal of medicine. 2018;378:625-635.*
6-Minute Walk Test (6MWT)	• An objective evaluation of functional exercise capability in ambulatory patients with later-onset (Type 2 or Type 3) SMA • Patient walks as far as possible in six minutes *Dunaway YS, Montes J, Kramer SS, et al. Six-minute walk test is reliable and valid in spinal muscular atrophy. Muscle Nerve. 2016; 54(5):836-842.*

CODING INFORMATION: *The codes listed in this clinical policy are for informational purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered. Coverage is determined by the benefit document. This list of codes may not be all inclusive and Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.*

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

HCPCS	Description
J2326	Injection, nusinersen, 0.1 mg (*Effective 1/1/18)

ICD-10	Description [For dates of service on or after 10/01/2015]
G12.0	Infantile spinal muscular atrophy, type I (Werdnig-Hoffman)
G12.1	Other inherited spinal muscular atrophy [includes types II, III (Kugelberg-Welander) and IV]

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Policy History	MCPC
Policy Developed Peer Review: AMR Peer Review Network. 2/13/2017. Practicing Physician. Board certified in Neurology, Pain Management	MCPC 2/16/2017
Policy Revised Peer Review: AMR Peer Review Network. Practicing Physician. Board certified in Neurology, Sleep Medicine. Date Completed: 5/2/2018.	MCPC 7/10/2018
Policy Revised Peer Review: AMR Peer Review Network. Practicing Physician. Board certified in Neurology, Sleep Medicine. Date Completed: 9/10/2019 Notable Revisions: Added the following criterion in 'Exclusions' section: • Use of nusinersen after gene replacement therapy • Concomitant use of nusinersen and onasemnogene abeparvovec (Zolgensma)	P&T Q4 2019

Revision AMR Peer Review Network. Practicing Physician. Board certified in Neurology, Sleep Medicine. Date completed: 6/22/2020 Notable criterion revisions: • Revised '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	P&T Q4 2020

NOTE: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Revisions.' Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer. The revisions noted below but may not be all-inclusive of all revised criteria and content in each policy; refer to MCP for all revisions and complete context.