Spinraza (nusinersen) Medical Drug Criteria Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
05-01-2025

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
SPINRAZA® (nusinersen) Intrathecal injection	Treatment of spinal muscular atrophy (SMA) in pediatric and adult patients		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Spinal Muscular Atrophy	Spinal muscular atrophy (SMA) is the second most common autosomal recessive neurodegenerative disorder, caused by deletion or loss of function mutation of the survival motor neuron 1 (SMN1) gene.(2,8) SMA is characterized by dysfunction and then loss of the alpha motor neurons in the spinal cord that causes progressive muscle atrophy and weakness.(10) There are two forms of survival motor neuron (SMN), SMN1 and SMN2, which are located on chromosome 5q13.2.(5) SMN1 is the primary gene responsible for functional production of SMN protein.(3) SMN1 can be absent because of deletion or SMN1-to-SMN2 conversion.(5) SMN2 preferentially excludes exon 7 during splicing and, as a result, produces only a small fraction of functional SMN protein as compared with SMN1. Because SMN2 produces a reduced number of SMN proteins, it can only partially compensate for the loss of SMN1 gene. SMA has an incidence of approximately 1 in 10,000 live births and a carrier frequency of approximately 1 in 54. It is one of the leading causes of infant mortality.(3) Molecular genetic testing of SMN1/SMN2 is highly reliable and is the standard tool for the diagnosis of SMA.(2,4,10) Genetic testing for homozygous deletion will confirm the disease in 95% of patients. Essentially all other patients with SMN-related SMA will be compound heterozygotes with a single SMN1 deletion and a mutation in the other SMN1 copy.(4) With newborn screening (NBS) becoming more widespread, infants can be diagnosed and receive early disease-modifying treatment, even before they become symptomatic. SMA newborns identified by NBS and before treatment initiation should be characterized by SMN2 copy number (probable Type), current motor function, age at symptom onset, and severity of symptoms. Early diagnosis and treatment will give infants with SMA the best outcomes and a healthier life.(9,10) SMA was historically classified into Types 0-4 based on age of onset of symptoms and motor milestone achievement. Applied retroactively, it was most applicable to older children and adults.(2,11) Type 0 is very rare with symptoms beginning prior to birth and survival being only a few months. Type 1 is the most common and severe form and usually diagnosed during the first six months of life. Type 2 is usually diagnosed after six months of age but before 2 years of age. Type 3, known as juvenile SMA, is typically diagnosed after 18 months of age and before 3 years of age. However, some SMA Type 3 patients can be diagnosed as late as the teenage years. Type 4 is very

	rare, less than 1% of cases, and usually symptoms appear as early as 18 years of age but most commonly after 35 years of age.(11) SMN2 copy number is predictive of phenotype severity. The more copies of SMN2, the milder phenotypic presentation.(10) For example, in a large German study, 80% of SMN Type 1 patients had two or less copies of SMN2, 82% with SMN Type 2 patients had three copies, and 96% of SMN Type 3 patients had 3 or 4 copies. The most severe is Type 0 with a single copy of SMN2. Infants with two or three SMN2 copies are likely to develop SMA Type 1 or 2. Type 4 usually has 4 or more SMN2 copies.(4,10) Therefore, determination of SMN2 copy number is a powerful predictor of disease and appropriate treatments.(10) With the approval of SMN-enhancing treatments and the addition of NBS, a dramatic changed in the natural history of SMA across all ages and has led to a shift in disease management.(11) According to the updated treatment algorithm from the SMA NBS Multidisciplinary Working Group, infants diagnosed through NBS with up to four SMN2 gene copies require immediate treatment. Patients with five (or more) SMN2 gene copies should be observed and screened for symptoms.(7,10,11) Guidelines recommend the use of age-appropriate function assessments to advise initiation and follow-up of drug therapy in SMA patients. They acknowledge that the tests vary in availability, physician expertise and preference, and the patient's ability, based on age, to participate. The function assessments that were considered for use in SMA patients were CHOP-INTEND, Hammersmith Infant Neurological Examination (HINE-2), Hammersmith Functional Motor Scale-Expanded (HFMSE), six-minute walk test (6MWT), Revised Upper Limb Module (RULM) test, and Bayley Scales of Infant and Toddler Development (BSID). Risdiplam efficacy trials utilized Bayley Scales of Infant and Toddler development, Third Edition (BSID-III), and Motor Function Measurement score (MFM32).(10)
Efficacy	The efficacy of SPINRAZA for the treatment of patients with symptomatic infantile-onset, later-onset, and presymptomatic SMA was evaluated in three clinical trials, Study 1 (ENDEAR NCT02193074), Study 2 (CHERISH NCT02292537), and Study 3 (NURTURE NCT02386553), respectively.(1) **ENDEAR** This was a multicenter, double-blind, randomized, sham-procedure controlled study to assess efficacy, safety and tolerability of SPINRAZA administered intrathecally (IT) to participants with infantile-onset SMA. Patients (n=121) were randomized 2:1 to receive either SPINRAZA or sham-procedure control. Key inclusion criteria included the following: onset of SMA symptoms before 6 months of age, age less than or equal to 7 months at the time of the first dose and two copies of the SMN2 gene.(1) The primary outcome assessed at the interim analysis (conducted on patients who died, withdrew, or completed at least 183 days of treatment) was proportion of responders [i.e., improvement in motor milestones according to section 2 of the Hammersmith Infant Neurologic Exam (HINE)] and was assessed at study day 183 and onwards. Treatment responders were defined as those with at least a 2-point increase in ability to kick, or at least a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking. Responders needed to exhibit improvement in more categories of motor milestones than worsening. An interim analysis of the results was evaluated among 82 patients who were eligible. A statistically significant percent of patients in the SPINRAZA arm achieved motor milestone response compared to those in the sham-procedure arm. The trial also assessed treatment effects using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), a tool that evaluates motor skills in patients with infantile-onset SMA.(1) The primary outcome assessed at the final analysis was time to death or permanent ventilations (greater than or equal to 16 hours ventilation/day continuously for greater than 21 days in the absence of an acute reversible event or tracheostomy). Statistically significant effects on event-free survival and overall survival were

observed in patients in the SPINRAZA group compared to those in the sham-control group. A 47% reduction in the risk of death or permanent ventilation was observed in the SPINRAZA group (p=0.005). Median time to death or permanent ventilation was not reached in SPINRAZA group and was 22.6 weeks in the sham-control group. A statistically significant 63% reduction in the risk of death was also observed (p=0.004). The final analysis also assessed the treatment effects on the CHOP-INTEND and are noted below.

Motor Milestone Response and CHOP-INTEND Results(1)

Endpoint	SPINRAZA-treated patients (n=73)	Sham-control patients (n=37)
Motor Milestone (HINE Section 2)		
Proportion achieving pre-defined motor milestone responder criteria (HINE section 2)*	37 (51%) p<0.0001	0 (0%)
CHOP-INTEND Improvement from Baseline*		
At least 4-points	52 (71%) p<0.0001	1 (3%)
CHOP-INTEND Worsening from Baseline **		
At least 4-points	2 (3%)	17 (46%)

* - Assessed at the later of Day 183, Day 302, and Day 394 Study Visit. According to HINE section 2: Greater than or equal to 2-point increase [or maximal score] in ability to kick, OR greater than or equal to 1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more

	categories of motor milestones than worsening), defined as a responder for this primary analysis. ** - Not statistically controlled for multiple comparisons **CHERISH** This was a multicenter, double-blind, randomized, sham-procedure controlled study of SPINRAZA in patients with later-onset SMA consistent with Type 2 SMA. Subjects were randomized 2:1 to receive SPINRAZA (n=84) or a sham-procedure control (n=42). The trial enrolled patients with onset of SMA symptoms at greater than 6 months of age and all patients had symptom onset by 21 months. The patients were required to be able to sit independently and to have never had the ability to walk independently. The primary endpoint was change in baseline HFMSE score at 15 months. HFMSE is a tool used to assess motor function in patients with SMA. Patients enrolled in the trial were required to have a baseline HFMSE score of greater than or equal to 10 and less than or equal to 54. A change of greater than or equal to 3 points in the HFMSE is estimated to represent a clinically meaningful improvement.(1) An interim analysis of the results at study month 15 was conducted among the trial participants. At the data cutoff date, 54 patients had completed the 15-month assessment and all patients had a HFMSE score that had been obtained at 6 months or later. In the interim analysis, SPINRAZA showed efficacy superior to that of the sham procedure; at the recommendation of their data and safety monitoring board, the trial was stopped early. All patients who had not had a 15-month assessment were invited to attend a visit that represented the end of the trial. The results showed a statistically significant change from baseline in the HFMSE score in the SPINRAZA group (4.0 (95% CI: 2.9-5.1)) compared to the sham-procedure control group (-1.9 (95% CI: -3.8-0.0)) (p=0.0000002). In the end of study analysis, the treatment difference in change from baseline to Month 15 in mean HFMSE score also was highly clinically and statistically significant (4.9 points: SPINRAZA, 3.9-point improvement; sham procedure control, 1.0-point decline; nominal). There were no treatment discontinuations due to adverse events. All patients who completed the CHERISH trial were invited to enroll in the open-label extension study in which all patients received SPINRAZA.(6) The authors of the CHERISH study published a follow-on article which showed that patients with Type 3 SMA may see benefit from SPINRAZA. A subset of the original CHERISH study's participants were over 18 months of age at time of symptom onset. In the final analysis, 57% of children in the SPINRAZA group compared with 26% in the control group had an increase from baseline to treatment month 15 in the HFMSE score of at least 3 points.(6) **NURTURE** This open-label uncontrolled trial was conducted in 25 presymptomatic SMA patients who had a genetic diagnosis of 5q SMA and 2 or 3 copies of SMN2. Patients were assessed with the World Health Organization (WHO) motor milestones, a set of 6 milestones in motor development that would be expected to be attained by 24 months of age in healthy children. An interim analysis was performed after all patients had received SPINRAZA for at least 14 months. At the time of the interim analysis, all patients receiving SPINRAZA before the onset of SMA symptoms survived without requiring permanent ventilation, and beyond what would be expected based on their SMN2 copy number. All 25 patients (100%) achieved the WHO motor milestone of sitting without support, and 22 patients (88%) achieved the milestone of walking with assistance. Of the 22 patients who were older than the age expected to have achieved the ability to walk independently, 17 (77%) achieved the milestone of walking alone (i.e., walking independently).(1)
Safety	SPINRAZA has no FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	SPINRAZA prescribing information. Biogen. April 2024.
2	Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscular Disorders*. 2017;28(2):103-115. doi:10.1016/j.nmd.2017.11.005
3	Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene Replacement Therapy for Spinal Muscular Atrophy. *N Engl J Med* 2017;377:1713-22.
4	Arnold WA, Kassar D, Kissel JT. Spinal Muscular Atrophy: Diagnosis and Management in a New Therapeutic Era. *Muscle Nerve* 2015 Feb;51(2):157-167. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4293319/.
5	Fang P, Li L, Zeng J, et al. Molecular Characterization and Copy Number of SMN1, SMN2 and NAIP in Chinese Patients with Spinal Muscular Atrophy and Unrelated Healthy Controls. *BMC Musculoskelet Disord.* 2015;16(1):11.
6	Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. *N Engl J Med* 2018;378:625-635. doi: 10.1056/NEJMoa1710504
7	Glascock J, Sampson J, Connolly AM, et al. Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2. *Journal of Neuromuscular Diseases*. 2020;7(2):97-100. doi:10.3233/jnd-190468
8	Keinath MC, Prior DE, Prior TW. (2021). Spinal Muscular Atrophy: Mutations, Testing, and Clinical Relevance. *The application of clinical genetics*, 14, 11-25. https://doi.org/10.2147/TACG.S239603.
9	Schroth M, Deans J, Arya K, et al. *Spinal Muscular Atrophy Update in Best Practices Recommendations for Diagnosis Considerations.*; 2024. doi:10.1212/CPJ.00200310
10	Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. *J Neuromuscul Dis*. 2018;5(2):145-158.
11	Spinal Muscular Atrophy - Symptoms, Causes, Treatment. National Organization for Rare Disorders. Updated April 2024. https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/.

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
J2326	Spinraza	nusinersen intrathecal soln	12 MG/5ML	M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Spinraza	nusinersen intrathecal soln	12 MG/5ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of spinal muscular atrophy (SMA) **AND** 2. The patient has a deletion or mutation at the survival motor neuron 1 (SMN1) gene on chromosome 5q confirmed by genetic testing (medical records required) **AND**

Module	Clinical Criteria for Approval
	3. The patient has a diagnosis of probable SMA type 1, 2, or 3 AND ONE of the following: A. If symptomatic, symptom onset was evident prior to 18 years of age **OR** B. If asymptomatic, the patient has no more than 4 copies of SMN2 **AND** 4. The patient has had at least one of the following baseline (prior to starting therapy with the requested agent) functional assessments based on patient age and motor ability: A. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) B. Hammersmith Infant Neurological Examination (HINE-2) C. Hammersmith Functional Motor Scale – Expanded (HFMSE) D. Six-minute walk test (6MWT) E. Bayley Scales of Infant and Toddler Development (BSID) F. Motor Function Measurement score (MFM32) G. Revised Upper Limb Module (RULM) test **AND** 5. The patient does NOT require invasive ventilation or tracheostomy **AND** 6. The patient has NOT received gene therapy for the requested indication (e.g., Zolgensma [onasemnogene abeparvovec-xioi]) **AND** 7. The patient will NOT be using the requested agent in combination with Evrysdi (risdiplam) for the requested indication **AND** 8. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 9. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 10. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval**: up to 6 months **NOTE:** For patients initiating therapy, approval will include 4 initial loading doses and 1 maintenance dose for the remainder of the 6 months per FDA labeling. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient was previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization from baseline (prior to starting therapy with the requested agent) with the requested agent as indicated by one of the following functional assessments based on patient age and motor ability: A. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) B. Hammersmith Infant Neurological Examination (HINE-2) C. Hammersmith Functional Motor Scale – Expanded (HFMSE) D. Six-minute walk test (6MWT) E. Bayley Scales of Infant and Toddler Development (BSID) F. Motor Function Measurement score (MFM32) G. Revised Upper Limb Module (RULM) test **AND** 3. The patient does NOT require invasive ventilation or tracheostomy **AND** 4. The patient has NOT received gene therapy for the requested indication (e.g., Zolgensma [onasemnogene abeparvovec-xioi]) **AND** 5. The patient will NOT be using the requested agent in combination with Evrysdi (risdiplam) for the requested indication **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**

Module	Clinical Criteria for Approval
	8. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** up to 12 months