Spinraza (nusinersen) Medical Drug Criteria Program Summary

POLICY REVIEW CYCLE

Effective Date	Date of Origin
05-01-2024	

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Spinraza® (nusinersen) Solution	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 bi-allelic loss or dysfunction 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) The SMN1 and SMN2 genes are all located on chromosome 5q13.2, an unstable chromosomal region that is prone to deletion, duplication, and gene conversion. There are two forms of survival motor neuron (SMN), SMN1 and SMN2, that differ by only five nucleotides.(9) SMN1 is the primary gene responsible for functional production of SMN protein. SMN1 produces a full-length transcript that encodes functional SMN protein.(3) SMN1 can be absent because of deletion or SMN1-to-SMN2 conversion.(9) The most common mutation causing SMA is a homozygous deletion of the SMN1 exon 7.(8) SMN2 preferentially excludes exon 7 during splicing and, as a result, produces only a small fraction of functional SMN protein as compared with SMN1.(3) Because SMN2 produces a reduced number of full-length transcripts, the number of SMN2 copies can modify the clinical phenotype and is an essential predictive factor.(3,8) About 94% of SMA patients have a homozygous deletion of SMN1 exon 7. SMA has an incidence of approximately 1 in 10,000 live births and a carrier frequency of approximately 1 in 54.(3)

SMA is classified into four subtypes (1-4) based on age of onset of symptoms and motor milestone achievement. This variability in the clinical phenotype is largely a result of the number of copies of the survival motor neuron 2 (SMN2) gene. The SMA type 1 (SMA1) phenotype is the most severe.(2) The presence of two copies of SMN2 is associated with SMA1. Infants with SMN1 bi-allelic deletions and two copies of SMN2 have a 97% risk of SMA1.(3)

Clinical Classification of SMA(8)

SMA Type	Number of SMN2 Copies	Percent of Cases	Age of Onset	Highest Achieved Motor Function	Natural Age of Death Prior to Disease

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					Modifying Therapy
0	1	Rare, less than 1%	Prenatal, at birth	Non-sitter, no head control	Death within weeks of birth
1	1-2	45%	0-6 months	Non-sitter	Death by age 2
2	3	20%	6-18 month	Sit independently, never stands or ambulates	Most alive at 25 years
3	3-4	30%	3a: 18 months-3 years 3b: 3-30 years	Ambulates independently	Normal lifespan
4	Greater than or equal to 4	Less than 5%	Greater than 30 years	Ambulates independently	Normal lifespan

The onset of symptoms for SMA1 occurs shortly after birth and prior to six months of age with a clinical hallmark of the inability to achieve independent sitting.(2) A historical cohort showed that the median age at symptom onset among infants with the disease was 1.2 months (range, 0 to 4 months).(3) Infants with SMA1 rapidly lose motor function and ultimately succumb to respiratory complications often within the first year of life. Studies of SMA1 infants with two SMN2 copies offered standard of care showed a median age of death or permanent ventilation (greater than or equal to 16h/day for at least 14 consecutive days) that ranged from 8 to 10.5 months.(2) Patients with SMA1 do not achieve major milestones in function and have a decline in function, as measured on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scale, which ranges from 0 to 64, with higher scores indicating better motor function. In a historical analysis of 34 patients with SMA1, all but one of the patients did not reach a score of at least 40 after 6 months of age. In another cohort, CHOP-INTEND scores decreased by a mean of 10.7 points from 6 months to 12 months of age.(3)

Molecular genetic testing is the standard tool for diagnosis of SMA. 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.(6) Guidelines recommend use of age-appropriate testing 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)

In addition to nusinersen, there are two additional FDA-approved therapies for SMA, Zolgensma and Evrysdi. Evrysdi, modifies pre-mRNA splicing of SMN2, increasing the production of SMN2. Evrysdi is administered as an oral solution dosed once daily.(4,8) Zolgensma is an SMN1 gene transfer via adenovirus vector dosed once via intravenous infusion.(5,8)

Efficacy	The efficacy of nusinersen was demonstrated in two double-blind, sham-procedure controlled trials in symptomatic infantile-onset and later-onset SMA patients (ENDEAR NCT02193074 and CHERISH NCT02292537). Its efficacy was further supported by

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open-label clinical trials conducted in pre-symptomatic and symptomatic SMA patients.(1)

ENDEAR

This was a phase III, double-blind, randomized, sham-procedure controlled study to assess efficacy, safety and tolerability of nusinersen administered intrathecally (IT) to participants with infantile-onset spinal muscular atrophy (SMA). Patients (n=121) were randomized 2:1 to receive either nusinersen 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 nusinersen 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%)

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	* - 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 phase III, double-blind, randomized, sham-procedure controlled study of nusinersen in patients with later-onset SMA consistent with type 2 SMA. Subjects were randomized 2:1 to receive nusinersen (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, nusinersen 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 nusinersen group (4.0

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	(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: nusinersen, 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 nusinersen.(7) The authors of the CHERISH study published a follow-on article which showed that patients with type III SMA may see benefit from nusinersen. 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 nusinersen 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.(7)
Safety	Spinraza has no FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Spinraza prescribing information. Biogen. February 2023.
2	Al-Zaidy S, Pickard AS, Kotha K, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. *Pediatr Pulmonol.* 2019;54(2):179-185.
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	Evrysdi prescribing information. Genentech, Inc. March 2023.
5	Zolgensma Prescribing Information. Novartis Gene Therapy, Inc. February 2023.
6	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/
7	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
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	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.
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.

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

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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) type 1, 2, or 3 **AND** 2. The patient's diagnosis was confirmed by genetic testing confirming the mutation or deletion of genes in chromosome 5q (medical records required) **AND** 3. Information has been provided that indicates the patient has two or more copies of SMN2 gene as determined by genetic testing **AND** 4. If the patient has ONE of the following: A. Type 1 or 2 and information has been provided that indicates the patient had onset of SMA symptoms at or before 21 months of age **OR** B. Type 3 and information has been provided that indicates the patient's onset of SMA symptoms occurred after 18 months of age **AND** 5. 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** 6. The patient does NOT require invasive ventilation or tracheostomy **AND** 7. The patient has not received gene therapy for the requested indication (e.g., Zolgensma [onasemnogene abeparvovec-xioi]) **AND** 8. The patient will NOT be using the requested agent in combination with Evrysdi (risdiplam) for the requested indication **AND** 9. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 10. 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** 11. 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. **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 **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)

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

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