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PHARMACY / MEDICAL POLICY – 5.01.574

Pharmacotherapy of Spinal Muscular Atrophy (SMA)

BCBSA Ref. Policy: 5.01.28

Effective Date:	Aug. 1, 2025	RELATED MEDICAL POLICIES:
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Replaces:	N/A	

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Introduction

Spinal muscular atrophy (SMA) is a rare disease that leads to muscle weakness and atrophy. SMA affects the muscles of the limbs and trunk. SMA is caused by changes to the survival motor neuron 1 gene (SMN1). This gene creates a protein called the survival motor neuron (SMN) protein. Too little of the SMN protein leads to muscle weakness that gets worse over time and muscles that waste away (atrophy). There are different types of SMA. Type 1 SMA, also known as Werdnig-Hoffman disease or infantile SMA, is the most severe form. Symptoms usually start before 6 months of age. The chance of survival to one year of age is 50 percent. Less severe forms are Type 2, also known as Dubowitz disease, and Type 3, or Kugelberg-Welander disease. Evrysdi (risdiplam), Spinraza (nusinersen), and Zolgensma (onasemnogene abeparvovec-xioi) are three treatments the Food and Drug Administration has approved for SMA. This policy discusses when the use of Evrysdi, Spinraza, and Zolgensma may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Evrysdi (risdiplam) **Managed under Pharmacy benefit**	**Evrysdi (risdiplam) may be considered medically necessary for the treatment of spinal muscular atrophy (SMA) when all the following criteria are met:** • The individual has a diagnosis of SMA Type 1, 2 or 3 attributed to the bi-allelic mutations of survival motor neuron 1 (SMN1) gene documented by genetic testing **AND** • Has not received Zolgensma (onasemnogene abeparvovec-xioi) **AND** • Medication is prescribed by a neurologist with expertise treating SMA **AND** • Evrysdi (risdiplam) will not used in combination with Spinraza (nusinersen) **AND** • The dose is limited to the following: ○ 0.15 mg/kg per day; less than 2 months of age ○ 0.2 mg/kg per day; 2 months to less than 2 years of age ○ 0.25 mg/kg per day; 2 years of age and older weighing less than 20 kg ○ 5 mg per day; 2 years of age and older weighing 20 kg or more **Note:** Although Types 2 and 3 manifest in childhood, treatment may be continued throughout the individual's lifetime.
Spinraza (nusinersen) **Managed under Medical benefit**	**Spinraza (nusinersen) may be considered medically necessary for the treatment of spinal muscular atrophy (SMA) when all the following criteria are met:** • The individual has a diagnosis of SMA Type 1, 2 or 3 attributed to the bi-allelic mutations of survival motor neuron 1 (SMN1) gene documented by genetic testing **AND** • Has not received Zolgensma (onasemnogene abeparvovec-xioi) **AND**

Drug	Medical Necessity
	• Medication is prescribed by a neurologist with expertise treating SMA **AND** • Spinraza (nusinersen) will not used in combination with Evrysdi (risdiplam) **Note:** Although Types 2 and 3 manifest in childhood, treatment may be continued throughout the individual's lifetime. **Note:** The recommended dosage is 12 mg (5mL) per administration. Treatment with Spinraza should be initiated with 4 loading doses. The first 3 loading doses should be administered at 14-day intervals. The 4th loading dose should be administered 30 days after the 3rd dose. The maintenance dose for Spinraza is administered once every 4 months thereafter.
Zolgensma (onasemnogene abeparvovec-xioi) **Managed under Medical benefit**	**Zolgensma (onasemnogene abeparvovec-xioi) may be considered medically necessary for the treatment of spinal muscular atrophy (SMA) when all the following criteria are met:** • The individual is aged less than 2 years at the time of infusion **AND** • Has a diagnosis of SMA attributed to the bi-allelic mutations of survival motor neuron 1 (SMN1) gene documented by genetic testing **AND** • Documented genetic test confirms 4 or fewer copies of the SMN2 gene **AND** • The individual does not have advanced SMA **AND** • Baseline anti-adeno-associated virus serotype 9 (AAV9) antibody levels are at most 1:50 **AND** • Medication is prescribed by a neurologist with expertise treating SMA **AND** • Zolgensma is administered as a one-time infusion **AND**

Drug	Medical Necessity
	• Prescriber attests to providing clinical outcome information within the appropriate provider portal as requested by the Company plan **Note:** The recommended dosage is 1.1 x 10^{14} vector genomes per kg of body weight administered as an intravenous infusion over 60 minutes

Drug	Investigational
As listed	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**
Evrysdi (risdiplam), Spinraza (nusinersen)	**All other uses of Evrysdi (risdiplam) and Spinraza (nusinersen) for conditions not outlined in this policy are considered investigational, including but not limited to:** • SMA that is not attributed to the bi-allelic mutations of SMN1 gene • SMA type 4 (adult onset) • Evrysdi or Spinraza use after Zolgensma infusion • Evrysdi and Spinraza used in combination with each other
Zolgensma (onasemnogene abeparvovec-xioi)	**All other uses of Zolgensma (onasemnogene abeparvovec-xioi) for conditions not outlined in this policy are considered investigational, including but not limited to:** • SMA that is not attributed to the bi-allelic mutations of SMN1 gene • Individuals with 5 or more copies of the SMN2 gene

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews and all other reviews for Evrysdi (risdiplam) and Spinraza (nusinersen) may be approved up to 12 months.** **Zolgensma (onasemnogene abeparvovec-xioi) may be approved as a one-time infusion.**

Length of Approval	
Approval	**Criteria**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews for Evrysdi (risdiplam) and Spinraza (nusinersen) may be approved up to 12 months when medical records show a positive clinical response to therapy as documented by:** • Improvement in functional measures appropriate to the individual's current abilities such as ambulation, arm strength, or pulmonary function. **Future re-authorization of Zolgensma (onasemnogene abeparvovec-xioi) beyond a one-time infusion is considered investigational.**

Documentation Requirements
• Initial approval requires chart notes documenting the diagnosis and genetic testing documenting bi-allelic mutations of SMN1 gene and the copies of SMN2 gene • Evrysdi (risdiplam) and Spinraza (nusinersen) re-authorization requires chart notes documenting progress, including functional measures appropriate to the individual's current abilities such as ambulation, arm strength, or pulmonary function.

Coding

Code	Description
HCPCS	
J2326	Injection, nusinersen (Spinraza), 0.1 mg
J3399	Injection, onasemnogene abeparvovec-xioi, per treatment, up to 5x10^15 vector genomes (Zolgensma)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Benefit Application

Evrysdi (risdiplam) is managed through the pharmacy benefit. Spinraza (nusinersen) and Zolgensma (onasemnogene abeparvovec-xioi) are managed through the medical benefit.

Consideration of Age

Age limits specified in this policy for Zolgensma are determined according to the FDA-approved indication. The use of Evrysdi and Spinraza for SMA type 1, 2, and 3 is based on the clinical trial experience as described in the full prescribing information of the FDA label. The individuals in these studies had or were likely to develop type 1, 2, or 3 SMA.

Availability

Zolgensma is only available at certified treatment centers.

Prescriber Attestation

Provider portals are used to capture clinical outcome information for individuals on select high-cost treatments, such as gene and cellular therapies. If an individual meets the medical necessity criteria as defined by this policy and is approved for treatment, the requesting prescriber must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

Evidence Review

Disease Background

Spinal muscular atrophy (SMA) is a rare recessive neurodegenerative disease that leads to muscle weakness and atrophy of the voluntary muscles of the limbs and trunk, due to the progressive loss of anterior horn cells of the spinal cord and brainstem nuclei.[2] SMA has an

incidence of about 1:10,000 live births and is the leading genetic cause of infant death. It has a carrier frequency estimated to be between 1:40 to 1:60

SMA is caused by the homozygous deletion of the survival motor neuron 1 gene (SMN1), which encode stable survival motor neuron (SMN) protein. The absence of enough SMN leads to increasing motor neuron dysfunction and progressive muscle weakness and atrophy. Cases are classified based on their severity and maximal achieved motor abilities, inversely correlating with the age of onset as well as the number of survival motor neuron 2 gene (SMN2) copies present. SMN2 encodes for SMN proteins that are less stable than those produced by SMN1 and do not have as lasting an impact on motor neuron function. SMN1 and SMN2 are nearly identical and encode the same protein. The critical sequence difference between the two genes is a single nucleotide in exon 7, which is thought to be an exon splice enhancer.

Type 1 SMA, also known as Werdnig-Hoffman disease or infantile SMA, is the most severe with symptomatic onset usually before 6 months and the probability of survival at 1 year is 50%.[2,7] Type 2 SMA is also called intermediate SMA or Dubowitz disease while type 3 SMA is also called juvenile SMA or Kugelberg-Welander disease, and both have slightly older age of onsets and more varied disease progression. Type 4 SMA is an adult onset form of SMA that is usually not symptomatic until later in life and rarely affects life expectancy.

Table 1. Clinical Classification of SMA

SMA Type	Age of Onset	Highest Achieved Motor Function	Natural Age of Death	Typical Number of SMN2 Copies
0	Prenatal/fetal	None	< 6 months	1
I	< 6 months	Sit with support only	< 2 years	2
II	6 – 18 months	Sit independently	> 2 years	3 or 4
III	> 18 months	Walk independently	Adulthood	3 or 4
IV	Adult (20s-30s)	Walk through adulthood	Adult	4 to 8

Evrysdi (risdiplam)

Risdiplam is an orally administered/available, centrally and peripherally distributed, pyridazine derived, small molecule designed to modify the splicing of the survival motor neuron (SMN2)

pre-mRNA and thus increase levels of functional SMN protein. The importance of adequate SMN protein levels which, are found to be depressed in SMA individuals, is in the maintenance of motor neurons which control muscle movement. This increase in functional SMN protein allows SMA individuals to achieve motor milestones and improve their functional abilities.

Evidence of Efficacy

In the SUNFISH phase II/III two-part, randomized, placebo-controlled trial of SMA Types 2/3, being the only placebo-controlled trial in progress to date, initial results showed an average increase from baseline after 12 months of treatment in MFM-32 score (an assessment of motor function) of 2.66 (±3.70) and a ≥3-point change (95% CI) for 58% (42-73%) for all individuals with available data in part one of the study (N=43). The second part of the trial saw statistically significant improvements at 12 months of treatment in MFM-32 and Revised Upper Limb Module scores with risdiplam in comparison with placebo of 1.55 (p=0.0156; N=170) and 1.59 (p=0.028; N=186), respectively. Caregiver reported SMA Independence Scale changes showed statistically significant improvement at 12 months compared to placebo. However, the individual reported improvement was not statistically significant. Minimal important difference (MID) information is unavailable for the previously mentioned outcome measures. However, an MID of 3 points is proposed for MFM-32 although the research supporting this is not yet available. At 12 months the difference from placebo for Hammersmith Functional Motor Score – Expanded was not statistically significant at 0.58 (p=0.3015) and failed to meet the MID of 3 points.

In the FIREFISH phase II/III two-part, open-label trial of SMA Type 1, initial results of part one (N=21) showed a median increase of 16 points in all individuals as well as a ≥4-point increase in 93% of individuals in their CHOP-INTEND score at 245 days of treatment. Clinical and statistical significance of these results are uncertain due to lack of placebo control as well as lack of MID for this outcome measure. At 245 days of treatment, a ≥40-point total score was achieved in 57% of individuals which is rare and considered clinically meaningful in comparison with known natural history data.

In the JEWELFISH phase II open-label trial of SMA individuals previously treated with other agents targeting SMN2 splicing, initial results for 4 individuals (12 months of treatment; Study enrollment N=174) shows a >2-fold increase in median SMN protein levels in the blood compared to baseline. Clinical significance of this change is uncertain at this point.

The RAINBOWFISH study is an open-label, single-arm, multicenter clinical study designed to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants up to 6 weeks of age (at first dose) who have been genetically diagnosed with SMA but do not

yet present with symptoms. At the time of an interim analysis, a total of 18 individuals with pre-symptomatic SMA were enrolled in Study 3. The efficacy in pre-symptomatic SMA individuals was evaluated in 7 individuals who had been treated with risdiplam for at least 12 months: four individuals had 2 copies of the SMN2 gene, 2 individuals had 3 copies, and 1 individual had 4 or more copies. Of these 7 individuals, the median age at first dose was 35 days (range: 16 to 40 days), 71% were female, 100% were Caucasian.

The 6 individuals with 2 or 3 copies of SMN2 achieved the following motor milestones as measured by the HINE-2 at Month 12: 6 (100%) individuals achieved sitting (5 individuals could pivot/rotate and 1 individual achieved stable sit); 4 (67%) individuals could stand (3 individuals could stand unaided and 1 individual could stand with support), and 3 (50%) individuals could walk independently. All 6 individuals were alive at 12 months without permanent ventilation.

Evidence of Safety

In the natural course of SMA common areas of complications include pulmonary issues, gastrointestinal/ digestive issues, and musculoskeletal issues among others. It is important to consider these issues in the natural course of SMA as well as the poor prognosis for SMA, especially in the case of earlier onset, in the evaluation of adverse events experienced during treatment and risk/benefit analysis.

In the SUNFISH phase II/III two-part, randomized, placebo-controlled trial of SMA Types 2/3, being the only placebo-controlled trial in progress to date, initial results showed no significant difference in serious adverse events (SAE) occurrence between the risdiplam and placebo groups at 20% (24/120) and 18.3% (11/60), respectively. The most common SAEs for individuals taking risdiplam were pneumonia (n=9), gastroenteritis (n=2), bacteremia (n=2), influenza (n=2), and pyrexia (n=2). This study did note a trend towards more grade 3-4 AEs in the risdiplam group compared to placebo was seen at 17.5% (21/120) and 13.3% (8/60), respectively.

In the FIREFISH phase II/III two-part, open-label trial of SMA Type 1, initial results of part one showed at least one SAE in 47.6% (10/21; most commonly pneumonia) and at least one grade 3-5 AE in 38.1% (8/21). In part one of this study 3 deaths have occurred due to respiratory complications which were considered unrelated to risdiplam use.

In the JEWELFISH phase II open-label trial of SMA individuals previously treated with other agents targeting SMN2 splicing, there have been no SAEs reported in 12 individuals (57-512 days of drug exposure; Study enrollment N=174)) with available data.

In the RAINBOWFISH study at the time of interim analysis, the study had enrolled 18 individuals with pre-symptomatic SMA between 16 and 40 days of age at the time of the first dose (weight range 3.1 to 5.7 kg). The median exposure duration was 8.7 months (range: 0.5 to 22.8 months). The safety profile of risdiplam in pre-symptomatic individuals in Study 3 is consistent with the safety profile for symptomatic SMA individuals treated with Evrysdi in clinical trials.

Spinraza (nusinersen)

Spinraza is a SMN2 directed antisense oligonucleotide that increases the production of complete SMN protein by increasing exon 7 inclusion into SMN2 mRNA transcripts (alternative splicing). The resulting protein resembles those produced by SMN1 and is more stable than regular SMN protein produced by SMN2. SMN protein is involved in the maintenance of motor neurons which control muscle movement. This allows SMA individuals to achieve motor milestones and improve their functional abilities.

In one clinical study, Spinraza resulted in platelet levels below the lower limit of normal in 6 of the 56 individuals who had normal baseline levels; however none of these individuals developed a sustained low platelet count. In two different studies, 17 out of 51 individuals and 36 out of 52 individuals on Spinraza had elevated urine protein. Common adverse reactions recorded in infantile SMA individuals included lower respiratory infection (43%), upper respiratory infection (39%), and constipation (30%), while common adverse reactions recorded in later onset individuals include headache (50%), back pain (41%), and post-lumbar puncture syndrome (41%) and were associated with the intrathecal administration.

Evidence of Efficacy

Currently, there are ten clinical trials that evaluate the use of Spinraza for SMA treatment, with efficacy endpoints focused on survival, growth parameters, electro-physiology, and motor function. The ENDEAR study, which provided much of the efficacy evidence, was a phase 3 sham procedure controlled study which depicted a 29% reduction in risk of death or permanent ventilation in the nusinersen group compared to the sham procedure controlled group. Mean improvements in motor milestones for the nusinersen group was observable starting at 2 months post treatment initiation with an increased difference from the sham control individuals as the study went on.

In another study, the interim analysis of 13 pre-symptomatic SMA individuals demonstrated that individuals treated with nusinersen exceeded expected outcomes with improvements in various

motor functions and motor milestone measures. Compared to the Pediatric Neuromuscular Clinical Research natural-history studies of SMA individuals that received standard of care, individuals with type 1 SMA treated with nusinersen had a significant differentiation in age at death or permanent ventilation as well as increased motor function and nerve response. The CS2 and CS12 studies showed additional milestone attainment and maintenance in type 2 and 3 SMA individuals who received nusinersen compared to the decline in milestone maintenance commonly seen in SMA individuals, with independent walking achieved in three individuals and increased mean ambulation. Nusinersen has not been studied in type 4 individuals.

Evidence of Safety

In the limited studies available, Spinraza has been shown to be generally safe, with most adverse events associated with the route of administration or the natural progression of SMA. Elevated urine protein and low platelet levels have been observed in a few studies with nusinersen; however, the coagulation abnormalities, thrombocytopenia, and renal toxicity associated with antisense oligonucleotides has not been observed with nusinersen though they are still listed as precautions. The majority of adverse events associated with nusinersen were mild to moderate in severity and mirrored events seen in the controlled historical groups, including respiratory distress, respiratory failure, pneumonia, acute respiratory failure, atelectasis, pneumonia aspiration, rhinovirus infection, and cardiorespiratory arrest.

Zolgensma (onasemnogene abeparvovec-xioi)

Zolgensma is a is a gene therapy that uses the adeno-associated virus serotype 9 vector (AAV9) to deliver a copy of the SMN gene to the nucleus of the individual's cells to replace the defective SMN1 gene without modifying the existing DNA of the individual.

Evidence of Efficacy

A Phase I, single-arm, open-label trial evaluated Zolgensma for the treatment of 15 individuals with genetically confirmed diagnosis of SMA1, homozygous SMN1 exon 7 deletions, and two copies of SMN2. Subjects were excluded if they had anti-AAV9 antibody titers > 1:50. Of The 15 study individuals, the three individuals in cohort 1 received a low dose of adeno-associated virus serotype 9 carrying SMN (6.7 x 1013 vg per kg of body weight) and the 12 individuals in cohort 2 received a high dose (2.0 x 1014 vg per kg of body weight). The mean age of individuals at the

time of treatment was 6.3 months (range 5.9 to 7.2) in cohort 1 and 3.4 months (range 0.9 to 7.9) in cohort 2. As a result of serum aminotransferase elevations in Individual 1 in cohort 1, which led to a protocol amendment, Individuals 2 to 15 received oral prednisolone at a dose of 1 mg per kg per day for approximately 30 days, starting 24 hours before the administration of gene therapy. The gene vector was delivered in normal saline that was infused IV during a period of approximately 60 minutes.

The primary outcome was the determination of safety on the basis of any treatment-related adverse events (AEs) of grade 3 or higher. The secondary outcome was the time until death or the need for permanent ventilatory assistance. Permanent ventilatory assistance was defined as at least 16 hours of respiratory assistance per day continuously for at least 14 days in the absence of an acute, reversible illness or a perioperative state. As of August 7, 2017, all the individuals had reached an age of at least 20 months and did not require permanent mechanical ventilation; the median age at their last pulmonary assessment was 30.8 months in cohort 1 and 25.7 months in cohort 2. At 29 months of age, one individual in cohort 1 required permanent ventilation because of hypersalivation. After salivary gland ligation, the requirement for the use of noninvasive ventilation was reduced by 25% to 15 hours per day.

Exploratory outcomes included motor-milestone achievements (particularly, sitting unassisted) and The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores. All the individuals in cohorts 1 and 2 had increased scores from baseline on the CHOP INTEND scale and maintained these changes during the study. Individuals in cohort 2 had mean increases of 9.8 points at 1 month and 15.4 points at 3 months ($P<0.001$ for both comparisons); 11 individuals attained and sustained scores of more than 40 points. No individuals in cohort 1 attained any motor milestones. A total of 11 of 12 individuals in cohort 2 were able to sit unassisted for at least 5 seconds, 10 for at least 10 seconds, and 9 for at least 30 seconds. A total of 11 achieved head control, 9 could roll over, and 2 were able to crawl, pull to stand, stand independently, and walk independently. Eleven individuals attained the ability to speak.

Evidence of Safety

As of August 7, 2017, a total of 56 serious adverse events were observed in 13 individuals in the two cohorts. Of these, 2 events were treatment-related grade 4 based on laboratory values. Individual 1 in cohort 1 had elevations in serum aminotransferase levels (31 times the ULN for ALT and 14 times the ULN for AST) without other liver-function abnormalities and without clinical manifestations. These elevations were attenuated by prednisolone treatment, which was subsequently administered to the remaining individuals. One individual in cohort 2 required

additional prednisolone to attenuate elevated serum ALT and AST levels. Of the 241 non-serious adverse events, 3 were deemed to be treatment-related and consisted of asymptomatic elevations in serum aminotransferase levels in 2 individuals. The most common adverse events were upper respiratory tract infection (73%), vomiting (53%), constipation (53%), pyrexia (47%), nasal congestion (40%), and gastroesophageal reflux (40%).

In October 2021 Zolgensma received a black box warning noting that acute serious liver injury, acute liver failure, and elevated aminotransferases can occur and that individuals with preexisting liver impairment may be at higher risk. Prior to infusion, assess liver function of all individuals by clinical examination and laboratory testing (eg, hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Corticosteroids are to be administered to all individuals before and after Zolgensma infusion and individuals are to have liver function monitored for at least 3 months after infusion.

National Institute for Health and Care Excellence

On July 24, 2019, the National Institute for Health and Care Excellence (NICE) issued technology appraisal guidance on nusinersen for treating spinal muscular atrophy. Nusinersen is recommended as an option for treating SMA only if people have pre-symptomatic SMA, or SMA types 1, 2 or 3 and the conditions laid out in the managed access agreement were followed.

On December 16, 2021, the NICE issued technology appraisal guidance on risdiplam for treating spinal muscular atrophy. Risdiplam is recommended as an option for treating 5q spinal muscular atrophy in people 2 months and older with a clinical diagnosis of SMA types 1, 2 or 3 or with pre-symptomatic SMA and 1 to 4 *SMN2* copies and the conditions laid out in the managed access agreement were followed.

On July 7, 2021, the NICE issued specialized technology appraisal guidance on onasemnogene abeparvovec for treating spinal muscular atrophy. Recommendations are summarized below.

Onasemnogene abeparvovec is recommended as an option for treating 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of type 1 SMA in babies, only if:

- They are 6 months or younger, or they are aged 7 to 12 months, and their treatment is agreed by the national multidisciplinary team. It is only recommended for these groups if permanent ventilation for more than 16 hours per day or a tracheostomy is not needed, and the company provides it according to the commercial arrangement.

- For babies aged 7 to 12 months, the national multidisciplinary team should develop auditable criteria to enable onasemnogene abeparvovec to be allocated to babies in whom treatment will give them at least a 70% chance of being able to sit independently.
- Onasemnogene abeparvovec is recommended as an option for treating presymptomatic 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene in babies. It is recommended only if the conditions in the managed access agreement are followed.

On April 19, 2023, the NICE issued a specialized technology appraisal guidance on onasemnogene abeparvovec for treating presymptomatic spinal muscular atrophy. Recommendations are summarized below.

- Onasemnogene abeparvovec is recommended as an option for treating presymptomatic 5q SMA with a biallelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene in babies aged 12 months and under. It is only recommended if the company provides it according to the commercial arrangement.

Institute for Clinical and Economic Review

The Institute for Clinical and Economic Review published a final report on comparative effectiveness and value of nusinersen and onasemnogene abeparvovec-xioi for spinal muscular atrophy on April 3, 2019, and subsequently on May 24, 2019, published an update following U.S. Food and Drug Administration (FDA) approval of onasemnogene abeparvovec-xioi.

Nusinersen

Based on the lack of relevant data, the report concluded that the evidence for nusinersen was insufficient for type 0 and IV spinal muscular atrophy.

- For infantile-onset spinal muscular atrophy, the Report concluded with high certainty that nusinersen provides a substantial net health benefit, and rate the evidence base as "superior" to standard care (A). Limitations included potentially limited generalizability, as Type I spinal muscular atrophy patients with more severe disease were underrepresented in the trials and may not adequately reflect the "real-world" patient population."
- For later-onset spinal muscular atrophy, the report concluded with moderate certainty that nusinersen provides a small or substantial net health benefit with a high certainty of at least

a small net health benefit and rate the evidence as "incremental or better" (B+). Limitations included potentially limited generalizability (trial population may not reflect the true patient population) lack of data on survival, ventilation, and event-free survival and long-term safety and durability of clinical benefit.

- For presymptomatic spinal muscular atrophy, the report concluded with moderate certainty of a small or substantial net health benefit with a high certainty of at least a small net health benefit and rate the evidence as "incremental or better" (B+).

Onasemnogene Abeparvovec-Xioi

The report only included and appraised the published evidence from the Phase I dose-finding study of onasemnogene abeparvovec-xioi. The authors did not rate the quality of this study because they do not conduct quality assessment of non-comparative studies.

- For type 0, later-onset (types II and III), type IV and presymptomatic spinal muscular atrophy, the Report concluded that the evidence for onasemnogene abeparvovec-xioi was insufficient due to lack of relevant data. The report also rated the evidence to be insufficient for comparison of onasemnogene abeparvovec-xioi versus nusinersen for infantile-onset spinal muscular atrophy due to lack of evidence.
- For infantile-onset spinal muscular atrophy, the report concluded with high certainty that onasemnogene abeparvovec-xioi provides a substantial net health benefit, and rate the evidence base as "superior" to standard care (A).
- In summarizing the uncertainties of the clinical evidence, the Institute for Clinical and Economic Review report noted considerable uncertainty in the generalizability of the results and in the long-term durability and tolerability of treatment. Further, the report notes additional uncertainty related to the possibility of loss of transgene expression over time and subsequent treatment pathway. The report also noted that some patients in the pivotal trial subsequently received nusinersen, but the effects of combination or sequential therapies have not been well studied.

Subsequent to the FDA approval of onasemnogene abeparvovec-xioi, the Institute for Clinical and Economic Review issued an update with a brief discussion of additional data/interim analyses from ongoing trials that were presented at the Muscular Dystrophy Association Clinical and Scientific Conference April 13-17, 2019, and American Academy of Neurology Annual Meeting May 4-10, 2019) and manufacturer press releases. In summary, the Institute for Clinical and Economic Review noted that the updated data are largely consistent with previously

available findings and as the data evolves and confirms the initial findings, the evidence rating may be revised.

Ongoing Clinical Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04488133 (RESPOND)[a]	A Study of Nusinersen Among Participants With Spinal Muscular Atrophy Who Received Onasemnogene Abeparvovec	46	Oct 2025
NCT04089566 (DEVOTE)[a]	Study of Nusinersen in Participants With Spinal Muscular Atrophy	145	Jun 2024
NCT05067790 (ASCEND)	A Phase 3b Study to Evaluate Higher Dose Nusinersen (BIIB058) in Patients With Spinal Muscular Atrophy Previously Treated With Risdiplam	45	Jun 2027
NCT03709784 (SAS)	Spinraza in Adult Spinal Muscular Atrophy (SAS)	148	Jan 2025
NCT04729907 (ONWARD)	Extension Study of Nusinersen (BIIB058) in Participants With Spinal Muscular Atrophy Who Previously Participated in a Study With Nusinersen	145	Jul 2026
NCT03421977 (START)[a]	Long-Term Follow-up Study for Patients From AVXS-101-CL-101	15	Dec 2033
NCT04042025[a]	Long-term Follow-up Study of Patients Receiving Onasemnogene Abeparvovec-xioi	85	Dec 2035
NCT05386680 (STRENGTH)	Phase IIIb, Open-label, Single-arm, Multi-center Study to Evaluate the Safety, Tolerability and Efficacy of OAV101 Administered Intrathecally to Participants With SMA Who Discontinued Treatment With Nusinersen or Risdiplam	28	Oct 2024
NCT05089656 (STEER)	A Randomized, Sham-controlled, Double-blind Study to Evaluate the Efficacy and Safety of Intrathecal OAV101 in Type 2 Spinal Muscular Atrophy (SMA) Patients Who Are ≥ 2 to < 18 Years of Age, Treatment Naive, Sitting, and Never Ambulatory	125	Oct 2024

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT05335876	Long-term Follow-up of Patients With Spinal Muscular Atrophy Treated With OAV101 IT or OAV101 IV in Clinical Trials	260	Oct 2039
NCT03779334 (RAINBOWFISH)	A Study of Risdiplam in Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy	25	Jun 2023
NCT03032172 (JEWELFISH)	A Study of Risdiplam (RO7034067) in Adult and Pediatric Participants With Spinal Muscular Atrophy	174	Jan 2022
NCT05522361 (RISE)	Risdiplam Exchange in Patients With Spinal Muscular Atrophy (SMA) Previously and Exclusively Treated With Nusinersen	10	Jan 2026
NCT05115110	A Study to Investigate the Safety and Efficacy of RO7204239 in Combination With Risdiplam (RO7034067) in Ambulatory Children With Spinal Muscular Atrophy	180	Dec 2026
NCT05232929 (WeSMA)	Long-Term Follow-Up Study of Patients With Spinal Muscular Atrophy Receiving Risdiplam Treatment	500	Feb 2029

NCT: national clinical trial; SMA: spinal muscular atrophy.

[a] Denotes industry-sponsored or cosponsored trial.

2018 Update

A literature search from 1/1/17 to 3/30/18 did not reveal new clinical data requiring change to the above criteria. Added reauthorization period and criteria.

2019 Update

Added criteria for Zolgensma (onasemnogene abeparvovec-xioi) which was approved by the FDA in May 2019. Reviewed prescribing information for Spinraza (nusinersen) and no new information was identified that would change coverage criteria.

2020 Update

Reviewed prescribing information for Zolgensma (onasemnogene abeparvovec-xioi) and Spinraza (nusinersen) and no new information was identified that would change coverage

criteria. Added criteria for Evrysdi (risdiplam) which is an oral medication that was approved by the FDA in August 2020 for the treatment of SMA in individuals 2 months of age and older.

2021 Update

Reviewed prescribing information for Evrysdi (risdiplam), Spinraza (nusinersen), and Zolgensma (onasemnogene abeparvovec-xioi). No new information was identified that would result in changes to policy statements. Added safety information to Zolgensma regarding a black box warning regarding acute serious liver injury and acute liver failure.

2021 Update

Reviewed prescribing information for Evrysdi (risdiplam), Spinraza (nusinersen), and Zolgensma (onasemnogene abeparvovec-xioi). Updated Evrysdi coverage criteria as the FDA approval for Evrysdi was expanded to include babies under 2 months of age with SMA based on interim efficacy and safety data from the RAINBOWFISH study. Updated Spinraza (nusinersen) criteria to include that Spinraza is prescribed by a neurologist with expertise treating SMA. All three drugs, Evrysdi, Spinraza, and Zolgensma now include identical language that the product is prescribed by a neurologist with expertise treating SMA.

2023 Update

Reviewed prescribing information of all drugs in this policy. Updated Zolgensma (onasemnogene abeparvovec-xioi) criteria to include coverage of individuals with 4 copies of the SMN2 gene.

2024 Update

Reviewed prescribing information of all drugs in this policy. No new information was identified that would result in changes to policy statements.

2025 Update

Reviewed prescribing information of all drugs in this policy. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Updated Zolgensma (onasemnogene abeparvovec-xioi) coverage criteria to require that the prescriber attest to providing clinical outcome information within the appropriate provider portal as requested by the Company plan.

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History

Date	Comments
04/01/17	New policy, approved March 14, 2017. Add to Prescription Drug section. Nusinersen (Spinraza®) may be considered medically necessary to treat SMA when criteria are met; all other uses are considered investigational.
07/01/17	Coding update; added HCPCS code C9489 (new code effective 7/1/17).
11/01/17	Interim Review, approved October 10, 2017. Clarified Spinraza® (nusinersen) criteria to include Type 1, 2, and 3 information.
01/01/18	Coding update; added HCPCS code J2326 (new code effective 1/1/18).
05/01/18	Annual Review, approved April 3, 2018. Added reauthorization criteria and duration. Removed HCPCS C9489 (it was terminated 1/1/18) and J3490 from policy.
09/21/18	Minor update. Added Consideration of Age statement.
07/01/19	Annual Review, approved June 11, 2019. Added criteria for Zolgensma (onasemnogene abeparvovec-xioi). Added HCPCS code J3590.
11/01/20	Annual Review, approved October 13, 2020. Added criteria for Evrysdi (risdiplam) for the treatment of SMA Type 1, 2 or 3.
02/01/21	Coding update, Added HCPCS code J3399 and removed HCPCS code J3590.
01/01/22	Annual Review, approved December 2, 2021. No changes to policy statements.
08/01/22	Annual Review, approved July 25, 2022. Updated Evrysdi (risdiplam) criteria removing requirement individual is 2 months of age or older as Everysdi is FDA approved in individuals less than 2 months of age. Updated Spinraza (nusinersen) criteria to include that Spinraza is prescribed by a neurologist with expertise treating SMA.
10/01/23	Annual Review, approved September 11, 2023. No changes to the policy statements.
01/01/24	Interim Review, approved December 12, 2023. Updated Zolgensma (onasemnogene abeparvovec-xioi) criteria to include coverage of individuals with 4 copies of the SMN2 gene.
09/01/24	Annual Review, approved August 26, 2024. No changes to policy statements.
04/01/25	Annual Review, approved March 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

Date	Comments
08/01/25	Interim Review, approved July 8, 2025. Updated Zolgensma (onasemnogene abeparvovec-xioi) coverage criteria to require that the prescriber attest to providing clinical outcome information within the appropriate provider portal as requested by the Company plan.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.