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# OHSU Drug Effectiveness Review Project Summary Report – FDA-Approved Treatments for Spinal Muscular Atrophy

**Date of Review:** February 2023 **Date of Last Review:** September 2019

**Current Status of PDL Class:**
See **Appendix 1**.

**Plain Language Summary:**

- This document is a summary of research report from the Oregon Health and Science University Drug Effectiveness Review Project (DERP). They studied all the medicines approved in the United States (U.S.) to treat spinal muscular atrophy.
- Spinal muscular atrophy is an inherited condition that destroys motor neurons, which are nerve cells that control muscles involved in speaking, walking, breathing, and swallowing. In spinal muscular atrophy, the muscles weaken over time and waste away. There are 3 types of spinal muscular atrophy: babies with Type 1 usually die before their second birthday. People with Type 2 and Type 3 may live full lives if their symptoms are less severe.
- There are 3 medicines approved in the U.S. to treat SMA: SPINRAZA (nusinersen), ZOLGENSMA (onasemnogene abeparvovec), and EVRYSDI (risdiplam). SPINRAZA is injected into the fluid surrounding the spinal cord every 4 months. ZOLGENSMA is administered only once into the veins. EVRYSDI is a pill that is taken by mouth every day for life.
- The DERP found all 3 medicines improve muscle function and decrease the risk of dying. None of the medicines help the breathing muscles, so some patients may still need a machine called a ventilator to help with breathing. EVRYSDI does not seem to help with a person's quality of life. Quality of life was not studied in people who took SPINRAZA or ZOLGENSMA, so it may be that none of the medicine affect a person's quality of life.
- Most of the side effects with SPINRAZA were because it is injected into the fluid around the spinal cord, which can cause headache, backpain, and nausea. ZOLGENSMA can hurt the liver, so people who receive this medicine must have their liver monitored with regular blood tests.
- Spinal muscular atrophy is a rare disease, so less than 100 people were studied in clinical trials. People in the trials were studied for up to 2 years so it is not clear how well these medicines work beyond 2 years. Currently, there is a longer study with ZOLGENSMA which will see how safe and effective it is after 5 years of receiving the medicine.
- Doctors who prescribe one of these medicines to a person enrolled in the Oregon Health Plan must show that certain criteria have been met to ensure the medicine is used safely and correctly before Medicaid will pay for it. This process is called prior authorization.

**Research Questions:**

1. What is the effectiveness of nusinersen (SPINRAZA), onasemnogene abeparvovec (ZOLGENSMA), and risdiplam (EVRYSDI) for treating spinal muscular atrophy (SMA)?
2. What are the harms of nusinersen, onasemongene abeparvovec, and risdiplam for treating SMA?

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3. What are the effectiveness and harms of co-treatment or sequential use of treatments approved by the U.S. Food and Drug Administration to treat SMA?

**Conclusions:**

- Nusinersen and risdiplam may reduce mortality (low certainty of evidence [CoE]), increase the probability of achieving a motor-milestone response (moderate CoE), and increase motor function (very low CoE) when compared to sham control groups in clinical trials of individuals with SMA.[1] Similar benefits in these outcomes were also observed in non-controlled, single-arm trials of onasemnogene abeparvovec in infants with SMA Type 1 (low CoE).[1]
- There is no evidence to suggest an effect on permanent ventilation (very low CoE) or quality of life (moderate CoE), versus control groups across all 3 treatments.[1]
- Nearly all individuals treated with intrathecal nusinersen experienced post-lumbar puncture AEs such as headache, back pain, and nausea.[1] Onasemnogene abeparvovec may increase the risk of hepatic injury, and treatment requires ongoing liver function monitoring.[1]
- Overall, evidence is limited by a small number of studies with moderate to high risk of bias, and study populations that may not be generalizable to all patients with SMA.[1] No head-to-head studies were identified. Uncertainties about the long-term benefits and harms of SMA treatments remain.[1]
- No clinical evidence is available to support the use of co-treatment or sequential SMA treatment.[1] Such approaches are considered experimental and investigational.[1]
- In May 2022, the FDA revised the risdiplam indication to treatment of SMA in pediatric and adult patients.[2] Dosing recommendations now include guidance for dosing infants less than 2 months of age.[2]

**Recommendations:**

- Clinical evidence does not support changes to the Practitioner-Managed Prescription Drug Plan (PMPDP).
- Combine prior authorization (PA) criteria for all 3 treatments into one document called “Spinal Muscular Atrophy Drugs” as presented in **Appendix 2** with updates to clarify duration of therapy and FDA-approved age ranges.
- Add pregnancy assessment in women of child-bearing age to risdiplam section of the PA criteria.

**Summary of Prior Reviews and Current Policy**

- The first medication FDA-approved for all types of SMA in both pediatric and adult populations was intrathecal nusinersen.[3] The Pharmacy and Therapeutics (P & T) Committee approved recommendations to implement clinical PA criteria to ensure appropriate utilization of nusinersen in July 2017. In September 2019, the P & T Committee approved recommendations to implement clinical PA criteria to ensure one-time administration of onasemnogene abeparvovec in appropriate SMA pediatric patients. In addition, clinical PA criteria for nusinersen was revised to include an assessment of onasemnogene abeparvovec administration prior to nusinersen initiation. After evaluating costs in executive session, the Committee recommended creating a class for SMA drugs, and designating onasemnogene abeparvovec as preferred and nusinersen as non-preferred on the PMPDP. In December 2020, risdiplam was reviewed by the P & T Committee and was designated as nonpreferred on the PMPDP with clinical PA criteria to ensure appropriate use.
- The preferred drug list (PDL) status for the SMA drugs is listed in **Appendix 1.** The PA criteria for all 3 SMA treatments is outlined in **Appendix 2.**
- From April 2021 to March 2022, 94 patients on the Oregon Health Plan (OHP) had a SMA-related diagnosis: 22 were in enrolled in the Fee-for-Service (FFS) program and the remaining individuals were enrolled in a coordinated care organization (CCO). During the same time frame, 20 patients in OHP had claims for nusinersen, 5 patients had claims for risdiplam, and one patient received onasemnogene abeparvovec. As of October 2022, 4 of these patients are no longer enrolled in OHP, 11 are enrolled in FFS and 11 are enrolled in CCOs.

- The Health Evidence Review Commission (HERC) has included SMA as a funded condition on lines 71, 292, 345, and 377.[4] In addition, SMA carrier screening for pregnant women is addressed in HERC Guideline Note D17.[4] Genetic screening for SMA (CPT 81239) is funded once in a lifetime.[4]

**Methods:**
The June 2022 SMA drug class report by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.[1] The original report is available to P & T Committee members upon request.

The purpose of the DERP reports is to compare the clinical effectiveness and harms of different drugs. DERP reports are not clinical practice guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

**Background:**
Spinal muscular atrophy is an autosomal recessive inherited neuromuscular disorder characterized by degeneration of motor neurons in the spinal cord, which results in progressive weakness, atrophy of skeletal muscles and hypotonia.[5] Disease severity ranges from progressive infantile paralysis and premature death to limited motor neuron loss and normal life expectancy.[6] The incidence of SMA is estimated at 1 in 10,000 live births.[7] SMA is the most common genetic cause of death in infants due to respiratory insufficiency.[8] The phenotype is extremely variable. Patients are classified as SMA type 0 through 4 based on age at onset and motor milestone achievement. SMA Type 1 is the most common (45%) and severe type of SMA and occurs primarily in infants under 6 months of age.[9] These infants cannot sit unsupported and usually die within the first 2 years of life due to respiratory failure or infection. The characteristics of each SMA type are described in **Table 1.**

**Table 1. SMA classification and characteristics**[5]

| SMA Type | SMN2 copy numbers | Age of Onset | Motor Function | Median Survival * | Incidence (per 100,000 live births) |
|---|---|---|---|---|---|
| 0 | 1 | Prenatal | Respiratory failure at birth | Less than 6 months | < 1% of cases |
| 1 (severe) | 2 | 0 to 6 months | Unable to sit or roll unassisted | <2 years | 3.2 – 7.1 (45% of cases) |
| 2 (intermediate) | 2 to 4 | 7 - 18 months | Able to sit, but unable to independently walk | >2 years (~70% still alive at age 25) | 1 – 5.3 (20% of cases) |
| 3 (mild) | 3 to 4 | >18 months | Able to independently stand and walk, which may decline with disease progression | Adulthood | 1.5 – 4.6 (30 % of cases) |
| 4 (adult) | 4 to 8 | 10 to 30 years | Ambulatory, may have mild muscle weakness | Adulthood | 5% of cases |

Spinal muscular atrophy is caused by biallelic deletions or mutations of the survival motor neuron (SMN1) gene on chromosome 5q13 which reduces the overall production of SMN protein.[9] The survival motor neuron protein is essential for motor neuron development and function.[9] The SMN gene region consists of a two almost identical genes: SMN1 and SMN2.[8] The lack of SMN1 in patients with SMA results in a disruption of SMN function which is partially compensated by SMN2 protein synthesis. SMN2 produces transcripts of SMN protein lacking exon 7 which results in an alternatively spliced, truncated, and nonfunctional SMN protein.[8] Due to an incomplete exclusion of exon 7 from SMN2 messenger ribonucleic acid (mRNA), only a small part (10–15%) of the mRNA transcripts contain

exon 7, resulting in a small proportion of normal SMN protein (5-10%).[8] The number of copies of SMN2 correlate with the functional status of patients with SMA.[8] Infants with SMN1 biallelic deletions and only two copies of SMN2 have a 97% risk of SMA type 1.[10] The presence of 3 or more copies of SMN2 is associated with milder SMA symptoms. As the number of SMN2 copies correlates inversely with disease severity, moderate increases in SMN protein levels may have significant beneficial effects.[11]

The standard diagnostic tool for SMA is genetic testing to assess for homozygous deletions or mutations in the SMN1 gene. In part because of SMA's rapid progression and the importance of early diagnosis to preserve motor functioning, the disease has been added to newborn screening in the United States.[12] Different methods for a newborn screening have been developed to diagnose SMA from DNA extracted from newborn blood spots, including a liquid microbead array to detect the homozygous SMN1 exon 7 deletion, a high-resolution DNA melting analysis with the possibility to identify SMN1 and SMN2 deletion as well as to quantify copy numbers of both genes, and a real-time polymerase chain reaction. Carrier testing is available and carrier frequency is estimated as 1:40 to 1:60 in the general population.[13] It is not possible to predict the severity of the SMA phenotype from carrier screening.

Due to the difficulties in quantifying motor abilities in individuals with SMA, several functional motor scales were developed to assess functional status in people with SMA. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) was developed by physical therapists to provide a standardized method for motor skill evaluation of neck, trunk, and limb strength of children with SMA Type 1.[14] CHOP INTEND was validated in a small population of children (n=27) with SMA aged 3 to 260 months (mean age = 49 months).[15] The Hammersmith Functional Motor Scale Expanded for SMA (HFMSE) was developed by physical therapists to assess individuals with SMA type 2 and 3.[16] The HFMSE motor assessment includes upper and lower limb activities as well as head and trunk control. Inter-rater reliability was tested on 35 children with an inter observer agreement greater than 99%.[16] The Hammersmith Infant Neurological Exam (HINE) was developed by pediatric neurologists to assist in assessment of neurologic function of infants between 2 and 24 months of age.[17] Sequential use of the HINE allows the identification of early signs of neuromotor disorders, whereas individual items are predictive of motor outcomes.[18] The HINE screening can be used as a tool to capture motor milestones in patients with SMA, including head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling or bottom shuffling, standing, and walking.[19] The Motor Function Measure 32 (MFM-32) is an ordinal scale used to assess patients with neuromuscular diseases. It is comprised of 32 items to evaluate physical function. There is no established minimal clinically important difference between point values on the MFM-32. The Revised Upper Limb Module (RULM) was designed to assist in evaluation of young children's ability to perform specific tasks such as lifting small objects, pushing buttons, or using a pencil. It has been validated for use in SMA assessments in a variety of settings. The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) is an assessment tool used to measure major clinical development issues in the early childhood years. Although not specific to SMA, the tool measures 5 standardized developmental domains: cognitive, language, motor, social-emotional, and adaptive behavior. The social-emotional and adaptive behavior portions are completed by parental questionnaire while the other 3 areas are administered with child interaction. This tool has not been validated in SMA patients. **Table 2** provides a summary of each tool, the intended population, and scoring.

**Table 2. Motor Function Exams for SMA**

| Instrument | Domain Evaluated | Intended Population | Number of Items | Grading Scale | Score Range | MCID |
|---|---|---|---|---|---|---|
| 6MWT | Aerobic capacity and endurance | Ambulatory patients with SMA | 1 item: the distance covered by walking a flat 25-meter course over a 6-minute period | N/A | N/A | 50 to 70 meters |

| | | | | | | |
|---|---|---|---|---|---|---|
| BSID-III | Evaluates cognitive, motor, and behavioral development | Infants aged 1 month to 42 months | 66 items for motor development | 0 = no response<br>1 = full response | Not scored, testing is to determine ability | N/A |
| CHOP-INTEND | Motor function | Infants with SMA Type 1 | 16 items scored 0 to 4 | 0 = no response<br>4 = full response | 0 to 64 | Unknown; clinical trials have used a change of ≥ 4 points |
| HFSME | Motor function | SMA Types 2 and 3 | 33 items scored 0 to 2 | 0 = no response<br>2 = full response | 0 to 66 | Change of ≥ 3 points |
| HINE-2 | Motor Milestones | All infants aged 2 months to 24 months | 8 milestones with:<br>• 3 items scored 0 to 4<br>• 4 items scored 0 to 3<br>• 2 items scores 0 to 2 | 0 = absence of activity<br>Increasing points correspond to an increased level of milestone achievement | 0 to 26 | Unknown; however, an increase of ≥ 1 point is unlikely in infants with SMA Type 1 |
| MFM-20 | Motor function across 3 domains: standing and transfer (D1), axial and proximal (D2), and distal (D3) | Children under 7 years of age with neuromuscular diseases | 20 items scored 0 to 3 | 0 = no response<br>3 = full response | 0 to 60 | MCID has not been established for SMA |
| MFM-32 | Motor function across 3 domains: standing and transfer (D1), axial and proximal (D2), and distal (D3) | Adults and children older than 7 years of age with neuromuscular diseases | 32 items scored 0 to 3 | 0 = no response<br>3 = full response | 0 to 96 | MCID has not been established for SMA |
| RULM | Upper extremity and ADL function | All individuals with SMA; commonly used to assess non-ambulatory individuals | 1 unscored entry item; serves as functional class identification.<br><br>19 items scored 0 to 2 | 0 = unable<br>2 = able, no difficulty | 0 to 37 | Unknown, can vary:<br>• SMA Type 2: 1.2 to 2.7 points<br>• SMA Type 3: 3 to 6 points<br>• Ambulatory SMA: 0.5 to 1 point<br>• Non-ambulatory SMA: 2 to 4 points |
| WHO MGRS Milestones | Motor milestones | Children from birth to 5 years of age | 6 milestones scored from 1 to 3, or 9 representing an | 1 = unable<br>3 = able<br>9 = unable to test | Not scored, testing is done to determine | N/A |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | inability to test the milestone | | motor milestone attainment | |

Abbreviations: 6MWT: 6-Minute Walk Test; ADL: activities of daily living; BSID-III: Bayley Scales of Infant and Toddler Development; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFSME: Hammersmith Functional Motor Scale Expanded for SMA; HINE-2: Hammersmith Infant Neuromuscular Examination, Section 2; MCID: minimal clinically important difference; MFM-20: Motor Function Measure, 20 items; MFM-32; Motor Function Measure, 32 items; N/A: not applicable; RULM: Revised Upper Limb Module; SMA: spinal muscular atrophy; WHO MGRS: World Health Organization Multicenter Growth Reference Study

Three medications are approved by FDA to treat SMA: nusinersen, onasemnogene abeparvovec, and risdiplam. In 2016, nusinersen was the first treatment approved for pediatric and adult patients with SMA.[3] It is an antisense oligonucleotide (ASO) which increases exon 7 inclusion in SMN2 mRNA leading to production of full-length SMN protein, which can partially compensate for mutations of the SMN1 gene.[3] Nusinersen must be delivered by repeated intrathecal injections every 4 months after the initial loading dose because ASOs do not efficiently cross the blood-brain barrier.[3] Onasemnogene abeparvovec received FDA approval in 2019.[20] Onasemnogene abeparvovec is an adeno-associated viral serotype 9 (AAV9) vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene.[20] The AAV9 vector is an ideal method of administering gene therapy because it has rapid onset of transgene expression, can cross the blood-brain barrier, is small in size with a simple structure, and has low immunogenicity.[21] Onasemnogene abeparvovec is a one-time intravenous treatment that is designed to deliver a functional SMN1 gene, potentially enabling the production of SMN protein, resulting in the normal development of motor neurons.[20] The safety and effectiveness of repeated administration of onasemnogene abeparvovec have not been evaluated. In addition, its use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been studied.[20] In 2020, risdiplam, an oral solution, received FDA approval to treat SMA.[2] Risdiplam is an SMN2 splicing modifier designed to promote the inclusion of exon 7 to produce full-length SMN2 mRNA, which results in an increased production of functional SMN protein from the SMN2 gene.[2] Risdiplam received FDA approval for the treatment of SMA in patients 2 months of age and older.[2] Dosing is weight-based and must be administered every day for lifetime.[2] The indications approved for all 3 treatments are broader than the populations studied in clinical trials.

**DERP Report Summary Findings:**

DERP has standardized methods for literature search and assessment, and these can be found detailed in the full report. The literature search for the DERP report was conducted through February 10, 2022.[1] Thirty-one publications met inclusion criteria: 4 randomized controlled trials (RCTs); 8 uncontrolled interventional trials; and 19 cohort studies.[1] All of the cohort studies evaluated nusinersen. **Table 3** summarizes the study details for the RCTs and uncontrolled interventional trials for nusinersen, onasemnogene abeparvovec, and risdiplam. Short-term follow-up, lack of comparator groups, and post-hoc modification of primary endpoints studied increased risk of biases in these studies.[1] All the RCTs were conducted by the drug manufacturers and authors of the RCTs reported conflicts of interest which may also increase risk of biases.[1] Assessment of clinically relevant outcomes (i.e., motor function, respiratory support) were limited to infants under 24 months of age with presymptomatic SMA, SMA Type 1, and SMA Type 2.[1] Risk ratios (RR), 95% confidence intervals (CI), and p-values were calculated by DERP authors using statistical software.

**Table 3. Randomized Controlled Trials and Uncontrolled Interventional Studies of FDA-approved Treatments for SMA[1]**

| Drug (BRAND NAME) | Trial Name | Sample Size | SMA Type | Age | Follow-Up | Risk of Bias |
|---|---|---|---|---|---|---|
| ***Randomized Controlled Trials*** | | | | | | |
| **Nusinersen (SPINRAZA)** | ENDEAR | Nusinersen, n=80<br>Sham control, n=41 | Infantile-onset[a] | 0 to 7 months | 13 months | High |
| | CHERISH | Nusinersen, n=84<br>Sham control n=42 | Later-onset[b] | 2 to 12 years | 15 months | Moderate |
| | EMBRACE | Nusinersen, n=14<br>Sham control n=7 | Infantile-onset[a] or Later-onset[b] | 0 to 4 years | 14 months | High |
| **Risdiplam (EVRYSDI)** | SUNFISH Part 2 | Risdiplam, n=120<br>Placebo, n=60 | Type 2 or Non-ambulatory Type 3 | 2 to 25 years | 12 months | Moderate |
| ***Uncontrolled Interventional Studies*** | | | | | | |
| **Nusinersen (SPINRAZA)** | CS1/CS10 | n=28 | Type 2 or 3 | 2 to 14 years | 14 months | High |
| | CS2/CS12 | n=28 | Later-onset[b] | 2 to 15 years | 36 months | High |
| | CS3A | n=20 | Infantile-onset[a] | 3 weeks to 7 months | 18 months | High |
| | NURTURE | n=25 | Presymptomatic | < 6 weeks | 24 months | High |
| **Onasemnogene abeparvovec (ZOLGENSMA)** | STR1VE | n=22 | Type 1 | < 6 months | 18 months | High |
| | STR1VE-EU | n=126 | Type 1 | < 6 months | 18 months | High |
| | START | n=15 | Type 1 | < 6 months | 24 months | High |
| | START LTFU[c] | n=13 | Type 1 | < 6 months | 60 months | High |
| **Risdiplam (EVRYSDI)** | FIREFISH Part 1 | n=21 | Type 1 | 1 to 7 months | 12 months | High |

*Notes:*
*a. Infantile-onset defined as symptom onset before 6 months of age*
*b. Later-onset defined as symptom onset after 6 months of age*
*c. START LFTU is an ongoing, observational follow-up study to the original START trial with 13 of the 15 original participants for up to 15 years*

*Abbreviations: FDA: Food and Drug Administration; LTFU: long term follow-up; SMA = spinal muscular atrophy*

**1. Effectiveness of Nusinersen, Onasemnogene Abeparvovec, and Risdiplam in Treating SMA**

Different outcomes including mortality, need for permanent ventilation, quality of life, motor-milestone response, and motor function were used to evaluate medication effectiveness across all the studies.[1]

*Mortality*

- In 2 RCTs (ENDEAR and EMBRACE; total enrollment=142) some evidence of reduced mortality risk was shown with nusinersen over sham control (low CoE).[1] In the ENDEAR trial, which was conducted in participants with infantile-onset SMA (i.e., SMA Types 1 and 2) the risk of mortality was reduced by 60% with nusinersen compared to control (RR 0.4; 95% CI 0.2 to 0.8; p=0.01; low CoE).[1] In contrast, in the EMBRACE trial which included participants

with later-onset SMA (i.e., SMA Types 2 and 3), nusinersen had no effect on mortality compared with sham control (RR 0.2; 95% CI 0.0 to 3.9; p=0.91; low CoE).[2]

- In 3 cohort studies of nusinersen, 3 deaths out of 312 participants (1%) were reported in children with SMA Type 1 after 2 years of treatment (low CoE).[1]
- In 3 uncontrolled trials of onasemnogene abeparvovec (STR1VE, STR1VE-EU, START), 2 deaths out of 70 participants (3%) were reported in infants with SMA Type 1 over 36 months of follow-up (low CoE).[1]
- In 1 uncontrolled trial of risdiplam (FIREFISH Part 1), 3 deaths out of 21 participants (14%) were reported in infants with SMA Type 1 at 12 months (low CoE).[1]

*Need for Permanent Ventilation*

- In one RCT (ENDEAR, n=122), nusinersen did not reduce the need for permanent ventilation compared to sham control (RR 0.7; 05% CI 0.4 to 1.3; p=0.28; very low CoE).[1]
- In 2 uncontrolled trials with nusinersen (CS3A, NURTURE) a small proportion of participants required permanent ventilation (range 0 to 15%; very low CoE).[1] However, participants in these trials had higher baseline motor scores, and 1 trial was in presymptomatic infants.[1]
- In 3 uncontrolled trials with onasemnogene abeparvovec (STR1VE, STR1VE-EU, START) a small proportion of participants required permanent ventilation (range 8 to 18%; very low CoE).[1]
- In one uncontrolled trial of risdiplam (FIREFISH Part 1) the need for permanent ventilation was observed in 80% of participants (very low CoE).[1]
- In 4 cohort studies of nusinersen no ventilatory support was needed in children with SMA Types 1 to 3 (very low CoE).[1]

*Quality of Life*

- In one RCT (SUNFISH Part 2, n=180) no evidence of an impact on quality of life was shown with risdiplam compared with placebo (RR 1.2; 95% CI 0.8 to 1.7; p=0.35; moderate CoE).[1]
- No RCTs or uncontrolled trials evaluated the effect of nusinersen or onasemnogene abeparvovec on quality of life.[1]
- In 3 cohort studies of nusinersen, subjective self-reported or caregiver-reported improvements in quality of life were noted in adults with SMA Types 2 to 4 after 14 months; by caregivers of children with SMA Types 1 and 2 after 1 year; and in children and adults with SMA Types 1 to 4 with up to 2 years of follow-up.[1]

*Motor-Milestone Response*

- In 3 RCTs (ENDEAR, EMBRACE, CHERISH; total enrollment = 268) some evidence of an improvement in motor-milestone response was noted with nusinersen compared with control (very low CoE).[1] Fifteen percent to 79% of infants and children with infantile-onset and later-onset SMA achieved motor-milestone response (very low CoE).[1] However, at baseline, 57% of subjects sat without support in 1 RCT and 100% sat with support and 24% walked without support in another RCT.[1]
    - ENDEAR: RR 38.9; 95% CI 2.4 to 617.7; p<0.01
    - EMBRACE: RR 2.7; 95% CI 0.8 to 9.1; p=0.04
    - CHERISH: RR 3.3; 95% CI 0.8 to 13.7; p=0.08
- In one uncontrolled trial of risdiplam, 67% of infants with SMA Type 1 achieved motor-milestone response (very low CoE) after 12 months of treatment.[1]
- In 2 uncontrolled trials of onasemnogene abeparvovec, 82% to 86% of infants with SMA Type 1 achieved motor-milestone response 18 months post-infusion (very low CoE).[1]

*Motor Function*

Across studies, various motor scales (**Table 2**) were used to assess change in motor function from pretreatment baseline.[1] The most common scales used were CHOP-INTEND, HFSME, and RULM.[1] Across all 3 treatments increases from CHOP-INTEND baseline score were observed, more frequently in those who began

treatment at a younger age.[1] When the HFSME score was used, mixed results were observed.[1] However, younger participants and those less severely affected (i.e., SMA Types 2 and 3) had greater improvements in HFSME scores from baseline.[1] When the RULM score was used, younger children and those less severely affected (i.e., SMA Types 2 and 3) treated with nusinersen demonstrated larger average gains from baseline.[1]

- In 2 RCTs of nusinersen (ENDEAR, CHERISH) and 1 RCT of risdiplam (SUNFISH Part 2) with a total enrollment of 428, some evidence of improved motor function in CHOP-INTEND and HFSME scores was observed with nusinersen and risdiplam compared with control (moderate CoE).[1]
    - Participants with a CHOP-INTEND score 4 points or more increased from baseline at 13 months in ENDEAR: Nusinersen 65% vs. Sham Control 2%; RR, 26.6; 95% CI 3.8 to 185.9; p<0.01.[1]
    - Participants with a HFSME score 3 points or more increased from baseline at 15 months in CHERISH: Nusinersen, 57% vs. Sham Control, 26%; Odds Ratio (OR), 6; 95% CI 2 to 15; p<0.001.[1]
    - HFSME score mean change from baseline (points) in SUNFISH Part 2: Risdiplam, 1.4 vs. Placebo, -0.2; Difference, 0.6; 95% CI -0.5 to 1.7; p=0.39.[1]
- In 1 uncontrolled trial of risdiplam (FIREFISH Part 1) 86% of participants showed a 4 point or greater increase in CHOP-INTEND scores from baseline at 12 months.[1]
- Gains from baseline HFMSE scores were reported in 7 cohort studies of nusinersen in children and adults with SMA Types 2 and 3. However, only 3 of 7 studies reported clinically significant meaningful gains (i.e., increase of 3 points or more).[1]
- No significant change in HFSME score from baseline was reported in 3 cohort studies of nusinersen in adults with SMA Types 2 and 3 and one cohort study of ambulatory children with SMA Types 1 to 3.[1]
- Two cohort studies of nusinersen in adults with SMA Types 2 and 3 who were able to sit at baseline reported meaningful gains in RULM scores.[1]
- No effect on RULM scores were reported in 2 cohort studies of nusinersen versus control of ambulatory adults with SMA Types 2 and 3 and 6 cohort studies of adults with SMA Types 2 to 4.[1]

**2. Harms of Nusinersen, Onasemongene Abeparvovec, And Risdiplam**

Reporting of harms included AEs, SAEs, and treatment withdrawals due to AEs or SAEs. Across all studies, the most commonly reported AEs regardless of treatment were fever, upper respiratory infections, coughing, and vomiting.[1] Serious adverse events were commonly due to respiratory events regardless of treatment and were more common in younger children and participants with SMA Type 1.[1] An increased risk of treatment-related SAEs due to elevated liver enzymes (i.e., serum aminotransferase) was observed with onasemnogene abeparvovec (low CoE).[1]

*Adverse Events*

- In 3 RCTs of nusinersen (ENDEAR, EMBRACE, CHERISH) and 1 RCT of risdiplam (SUNFISH Part 2) with a total enrollment of 449, no evidence of an effect on the risk of experiencing one or more AEs was observed with nusinersen or risdiplam over control (moderate CoE).[1]
    - ENDEAR: RR 1.0; 95% CI 0.9 to 1.1; p=0.50
    - EMBRACE: RR 1.2; 95% CI 0.9 to 1.6; p=0.33
    - CHERISH: RR 0.9; 95% CI 0.9 to 1.0; p=0.08
    - SUNFISH Part 2: RR 1.0; 95% CI 0.9 to 1.1; p=0.83
- Across all 3 treatments, at least one AE was experienced by 86% to 100% of participants in 4 RCTs and 89% to 100% of participants in 8 uncontrolled trials.[1]
- In nusinersen studies, AEs relating to lumbar puncture (i.e., nausea) were frequently reported across all ages and SMA subtypes. Post-lumbar puncture headache was reported more frequently by adults in cohort studies (moderate CoE).[1]

- In 3 uncontrolled studies of onasemnogene abeparvovec, 27% to 73% of participants experienced treatment-related AEs due to elevated liver enzymes (i.e., serum aminotransferase) (moderate CoE).[1]

*Incidence of Adverse Events Leading to Treatment Discontinuation*

- Treatment discontinuation due to AEs was infrequent with nusinersen in 2 RCTs, 3 uncontrolled trials, and 4 cohort studies (moderate CoE).[1]
- Treatment discontinuation due to AEs was not reported for risdiplam or onasemnogene abeparvovec.[1]

*Serious Adverse Events*

- In 3 RCTs of nusinersen (ENDEAR, EMBRACE, CHERISH) and one RCT of risdiplam (SUNFISH Part 2) (total, n=449), no evidence of an effect on the risk of experiencing one or more SAEs was observed with nusinersen or risdiplam over control (low CoE).[1]
    - ENDEAR: RR, 8; 95% CI 0.7 to 0.9; p=0.01
    - EMBRACE: RR, 1.5; 95% CI 0.6 to 3.8; p=0.40
    - CHERISH: RR, 0.6; 95% CI 0.3 to 1.1; p=0.13
    - SUNFISH Part 2: RR, 1.1; 95% CI 0.6 to 2.1; p=0.80

**3.Co-Treatment or Sequential Treatment**

One high risk of bias cohort study provided evidence for the effectiveness and harms of co-treatment or sequential treatment in 76 children under 5 years of age who received nusinersen for a mean of 12 months before receiving a single infusion of onasemnogene abeparvovec.[1] Fifty-eight of 76 participants (76%) received pre-treatment with nusinersen.[1] Clinically meaningful gains from baseline CHOP-INTEND scores (i.e., an increase of $\geq$ 4 points) were observed in nusinersen-naïve and nusinersen-treated children 6 months post-infusion.[1] The efficacy and harms of co-treatment or sequential treatment with SMA therapies is unknown and considered to be investigational.[1]

**New Indications:**

When risdiplam (EVRYSDI) was initially approved in August 2020, the indication was for treatment of SMA in patients 2 months of age and older.[22]
In May 2022, the FDA revised the indication to treatment of SMA in patients less than 2 months of age.[2] Dosing recommendations now include guidance for dosing infants less than 2 months of age.[2]

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**Appendix 1:** Current Preferred Drug List

| Generic | Brand | Route | Form | PDL |
|---|---|---|---|---|
| Onasemnogene abeparvovec-xioi | ZOLGENSMA | IV | KIT | Y |
| Nusinersen sodium/PF | SPINRAZA | IT | VIAL | N |
| Risdiplam | EVRYSDI | PO | SOLN | N |

# Spinal Muscular Atrophy Drugs (Nusinersen-Retired)

**Goal(s):**
- Approve nusinersen (SPINRAZA), onasemnogene abeparvovec (ZOLGENSMA), or risdiplam (EVRYSDI) conditions supported by evidence of benefit (e.g., spinal muscular atrophy).

**Length of Authorization:**
- Nusinersen: Up to 8 months for initial approval and up to 12 months for renewal.
- Onasemnogene abeparvovec: Once in a lifetime dose.
- Risdiplam: Up to 6 months for initial approval and 12 months for renewal.

**Requires PA:**
- Nusinersen (billed as a pharmacy or physician administered claim)
- Onasemnogene abeparvovec (billed as a pharmacy or physician administered claim)
- Risdiplam (billed as pharmacy claim)

**Covered Alternatives:**
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

**Table 1. FDA-Approved Dosing For Risdiplam**

| Age and Body Weight | Recommended Daily Dose of Risdiplam |
|---|---|
| Less than 2 months of age | 0.15 mg/kg |
| 2 months to less than 2 years of age | 0.2 mg/kg |
| 2 years of age and older weighing less than 20 kg | 0.25 mg/kg |
| 2 years of age and older weighing 20 kg or more | 5 mg |

| Approval Criteria | | |
|---|---|---|
| 1. What diagnosis is being treated? | Record ICD-10 code. Go to #2 | |
| 2. Is this a request for continuation of nusinersen or risdiplam therapy?<br><br>Note: Onasemnogene abeparvovec is only approved as a single, one-time dose per lifetime | **Yes:** Go to **Renewal Criteria** | **No:** Go to #3 |
| 3. Does the patient have a diagnosis of spinal muscular atrophy (SMA), confirmed by SMN1 (chromosome 5q) gene mutation or deletion AND at least 2 copies of the SMN2 gene as documented by genetic testing? | **Yes:** Go to #4 | **No:** Pass to RPh. Deny; medical appropriateness. |
| 4. Is the requested medication prescribed by a pediatric neurologist or a provider with experience treating SMA? | **Yes:** Go to #5 | **No:** Pass to RPh. Deny; medical appropriateness |
| 5. Is the patient ventilator-dependent (using at least 16 hours per day on at least 21 of the last 30 days)?<br><br>Note: This assessment does not apply to patients who require ventilator assistance | **Yes:** Pass to RPh. Deny; medical appropriateness | **No:** Go to #6 |
| 6. Is a baseline motor assessment appropriate for age and/or intended population available such as one of the following assessments?<br>• Hammersmith Infant Neurological Examination, Section 2 (HINE-2)<br>• Hammersmith Functional Motor Scale (HFMSE)<br>• Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)<br>• The Motor Function Measure 32 items (MFM-32)<br>• Upper Limb Module (ULM) | **Yes:** Document date and assessment results<br>Date: _____<br>Assessment:_____<br>Results:_____<br><br>Go to #7 | **No:** Pass to RPh. Deny; medical appropriateness. |

| Approval Criteria | | |
|---|---|---|
| 7. Has the patient had previous administration of onasemnogene abeparvovec (ZOLGENSMA), either in a clinical study or as part of medical care? | **Yes:** Pass to RPh. Deny; medical appropriateness | **No:** Go to #8 |
| 8. Is the request for risdiplam? | **Yes**: Go to #9 | **No**: Go to #13 |
| 9. Is the prescribed dose within the limits defined in Table 1? | **Yes:** Go to #10 | **No:** Pass to RPh. Deny; medical appropriateness.<br><br>Recommended FDA-approved dosage is determined by age and body weight. |
| 10. In people of child-bearing potential, is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant? | **Yes:** Go to #11 | **No:** Pass to RPh. Deny; medical appropriateness |
| 11. Is the patient on concomitant therapy with nusinersen? | **Yes:** Pass to RPh. Deny; medical appropriateness**.** | **No:** Go to #12 |
| 12. For able patients, is there baseline documentation of pulmonary function measured by spirometry (FEV1, FVC, etc) or other validated pulmonary function test? | **Yes:** Document baseline results.<br><br>Approve for 6 months.<br><br>If approved, a referral will be made to case management by the Oregon Health Authority. | **No:** Pass to RPh. Deny; medical appropriateness. |
| 13. Is the request for nusinersen? | **Yes**: Go to #14 | **No**: Go to #15 |

| Approval Criteria | | |
|---|---|---|
| 14. Is the patient on concomitant therapy with risdiplam? | **Yes:** Pass to RPh. Deny; medical appropriateness**.** | **No:** Approve for up to 8 months. |
| 15. Is the request for onasemnogene abeparvovec? | Yes: Go to #16 | No: Pass to RPh. Deny; medical appropriateness |
| 16. Is the patient less than 2 years of age? | **Yes:** Go to #17 | **No:** Pass to RPh. Deny; medical appropriateness |
| 17. Have the following labs been obtained:<br><br>a) a baseline platelet count AND<br>b) baseline liver function tests (AST, ALT, total bilirubin, and PT) AND<br>c.) baseline troponin-I | **Yes:** Go to #18 | **No:** Pass to RPh. Deny; medical appropriateness |
| 18. Does the patient have a prescription on file for 30 days of on oral corticosteroid to begin one day before infusion of onasemnogene abeparvovec? | **Yes:** Approve for one time infusion | **No:** Pass to RPh. Deny; medical appropriateness |

| Renewal Criteria | | |
|---|---|---|
| 19. Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment? | **Yes:** Go to #2 | **No:** Pass to RPh; Deny medical appropriateness |

| Renewal Criteria | | |
|---|---|---|
| 20. Has the patient shown a positive treatment response in one of the following areas?<br>• Documented improvement from the baseline motor function assessment score with more areas of motor function improved than worsened<br>-OR-<br>• Documentation of clinically meaningful stabilization, delayed progression, or decreased decline in SMA-associated signs and symptoms compared to the predicted natural history trajectory of disease<br>-OR-<br>• Documentation of an improvement or lack of decline in pulmonary function compared to baseline | **Yes:** Approve for 12 months | **No:** Pass to RPh; Deny; medical appropriateness. |

*P&T Review: 2/23 (DM); 9/19 (DM); 7/17; 3/17*
*Implementation: 4/1/23; 11/1/19: 9/1/17; 5/17*

## Onasemnogene abeparvovec (Zolgensma®) - RETIRE

- **Goal(s):** Approve onasemnogene abeparvovec for funded OHP conditions supported by evidence of benefit (e.g., spinal muscular atrophy).

**Length of Authorization:**
- Once in a lifetime dose

**Requires PA:**
Onasemnogene abeparvovec (pharmacy and physician administered claims)

**Covered Alternatives:**
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

| Approval Criteria | | |
|---|---|---|
| 1.What diagnosis is being treated? | Record ICD10 code. | |
| 2. Is the medication prescribed by or in consultation with a physician who specializes in treatment of spinal muscular atrophy (SMA) such as pediatric neurologist? | **Yes:** Go to #3 | **No:** Pass to RPh. Deny; medical appropriateness |
| 3. Is the patient less than 2 years of age? | **Yes:** Go to #4 | **No:** Pass to RPh. Deny; medical appropriateness |
| 4. Does the patient have a SMA diagnosis, confirmed by SMN1 gene mutation or deletion… [is missing or not functional by genetic documentation of fewer than 4 copies of SMN2 AND at least one of the following]:<br>• Homozygous gene deletion or mutation of SMN1 gene (e.g., homozygous deletion of exon 7 at locus 5q13);<br><br>**-OR-**<br>• Compound heterozygous mutation of SMN1 gene (e.g., deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 (allele 2) | **Yes:** Go to #5 | **No:** Pass to RPh. Deny; medical appropriateness |
| 5. Does the patient have advanced SMA* (complete paralysis of the limbs, permanent ventilator dependence)?<br><br>*Note FDA label states efficacy has not been established in these patients | **Yes:** Pass to RPh. Deny; medical appropriateness | **No:** Go to #6 |

| Approval Criteria | | |
|---|---|---|
| 6. Has baseline motor ability been documented via:<br>• Hammersmith Infant Neurological Examination, Section 2 (HINE-2)<br>• Hammersmith Functional Motor Scale (HFSME)<br>• Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)<br>• The Motor Function Measure 32 items (MFM-32)<br>• Upper Limb Module (ULM) | **Yes:** Go to #7 | **No:** Pass to RPh. Deny; medical appropriateness |
| 7. Has the individual been screened for viral infection? | **Yes:** Go to #8 | **No:** Pass to RPh. Deny; medical appropriateness |
| 8. Is the baseline adeno-associated virus vector (AAV) 9 antibody titer < 1:50?<br><br>Note: Efficacy has not been established in this population and high anti-AAV9 antibody titers are expected to limit efficacy of therapy. | **Yes:** Go to #9 | **No:** Pass to RPh. Deny; medical appropriateness |
| 9. Have the following baseline labs been obtained:<br>c) Platelet count;<br>AND<br>d) Liver function tests (AST, ALT, total bilirubin, and PT);<br>AND<br>e) Troponin-I | **Yes:** Go to #10 | **No:** Pass to RPh. Deny; medical appropriateness |
| 10. Does the patient have a prescription on file for 30 days of on oral corticosteroid to begin one day before infusion of onasemnogene abeparvovec? | **Yes:** Go to #11 | **No:** Pass to RPh. Deny; medical appropriateness |
| 11. Is the patient currently receiving nusinersen? | **Yes:** Go to #12 | **No:** Go to #13 |

| Approval Criteria | | |
|---|---|---|
| 12. Are there plans to discontinue nusinersen? | **Yes:** Go to #13 | **No:** Pass to RPh. Deny; medical appropriateness |
| 13. Is there attestation that the patient and provider will comply with case management required by the Oregon Health Authority?<br><br>Case management includes follow-up assessment to assess treatment success, monitoring, and adverse events. | **Yes:** Approve one time infusion | **No:** Pass to RPh. Deny; medical appropriateness |

*P&T/DUR Review: 2/23 (DM); 9/19 (DM)*
*Implementation: 4/1/23 (retired); 11/1/19*

## Risdiplam- RETIRE

**Goal(s):**

- Approve risdiplam for funded OHP conditions supported by evidence of benefit (e.g., spinal muscular atrophy).

**Length of Authorization:**

- 6 months

**Requires PA:**

- Risdiplam

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

**Table 1**

| Age and Body Weight | Recommended Daily Dosage |
|---|---|
| Less than 2 months of age | 0.15 mg/kg |

| Age and Body Weight | Recommended Daily Dosage |
|---|---|
| 2 months to less than 2 years of age | 0.2 mg/kg |
| 2 years of age and older weighing less than 20 kg | 0.25 mg/kg |
| 2 years of age and older weighing 20 kg or more | 5 mg |

| Approval Criteria | | |
|---|---|---|
| 1. What diagnosis is being treated? | Record ICD10 code. | |
| 2. Is this a request for continuation of therapy approved by the FFS program? | **Yes**: Go to **Renewal Criteria** | **No:** Go to #3 |
| 3. Is the prescribed dose within the limits defined in Table 1? | **Yes:** Go to #4 | **No:** Pass to RPh. Deny; medical appropriateness.<br><br>Recommended FDA-approved dosage is determined by age and body weight. |
| 4. Does the patient have a diagnosis of spinal muscular atrophy (SMA), confirmed by SMN1 (chromosome 5q) gene mutation or deletion AND at least 2 copies of the SMN2 gene as documented by genetic testing? | **Yes:** Go to #5 | **No:** Pass to RPh. Deny; not funded by the OHP. |
| 5. Is the patient experiencing symptoms of SMA? | **Yes:** Go to #6 | **No:** Pass to RPh. Deny; medical appropriateness**.** |
| Does the patient have advanced SMA disease (ventilator dependence >16 hours/day or tracheostomy)? | **Yes:** Pass to RPh. Deny; medical appropriateness | **No:** Go to #7 |

| Approval Criteria | | |
|---|---|---|
| 6. Has the patient had previous administration of onasemnogene abeparvovec (ZOLGENSMA), either in a clinical study or as part of medical care? | **Yes:** Pass to RPh. Deny; medical appropriateness**.** | **No:** Go to #8 |
| 7. Is the patient on concomitant therapy with a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy? | **Yes:** Pass to RPh. Deny; medical appropriateness**.** | **No:** Go to #9 |
| 8. Is the drug being prescribed by a pediatric neurologist or a provider with experience treating SMA? | **Yes:** Go to #10 | **No:** Pass to RPh. Deny; medical appropriateness**.** |
| 9. Is a baseline motor assessment appropriate for age and/or intended population available such as one of the following assessments?<br>• Hammersmith Infant Neurological Examination, Section 2 (HINE-2)<br>• Hammersmith Functional Motor Scale (HFSME)<br>• The Motor Function Measure 32 items (MFM-32)<br>• Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)<br>• Upper Limb Module (ULM) or Revised Upper Limb Module (RULM) | **Yes:** Document baseline results.<br><br>Go to #11 | **No:** Pass to RPh. Deny; medical appropriateness**.** |
| 10. For able patients, is there baseline documentation of pulmonary function measured by spirometry (FEV1, FVC, etc) or other validated pulmonary function test? | **Yes:** Document baseline results.<br><br>Approve for 6 months.<br><br>If approved, a referral will be made to case management by the Oregon Health Authority. | **No:** Pass to RPh. Deny; medical appropriateness. |

| Renewal Criteria | | |
|---|---|---|
| 1. Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment? | **Yes:** Go to #2 | **No:** Pass to RPh; Deny medical appropriateness |
| 2. Has the patient shown a positive treatment response in one of the following areas?<br>• Within one month of renewal request, documented improvement from the baseline motor function assessment score with more areas of motor function improved than worsened<br>**-OR-**<br>• Documentation of clinically meaningful stabilization, delayed progression, or decreased decline in SMA-associated signs and symptoms compared to the predicted natural history trajectory of disease | **Yes:** Approve for additional 6 months. | **No:** Pass to RPh. Deny; medical appropriateness. |

*P&T/DUR Review: 2/23 (DM); 12/20 (DE)*
*Implementation: 4/1/23 (retired); 1/1/2021*