

Therapeutic Class Overview

Spinal Muscular Atrophy (SMA) Agents

INTRODUCTION

- Spinal muscular atrophy (SMA) is a serious neuromuscular disease characterized by the degeneration of motor neurons in the spinal cord and brainstem, leading to progressive muscular atrophy and weakness (*Genetics Home Reference 2020, Mercuri et al 2018[a]*). SMA is caused by an inherited genetic mutation, and is the most common genetic cause of infant mortality (*Bodamer 2020*).
- SMA is an autosomal recessive inherited disorder. The overall incidence is between 4 and 10 per 100,000 live births, and 1 person in 50 to 90 is a carrier of a mutation that can cause SMA (*Bodamer 2020*).
- The *SMN1* gene is responsible for the production of SMN protein, which is ubiquitously expressed in all cells throughout fetal and post-natal development. Deletion or mutations in the *SMN1* gene lead to a shortage of the protein. Without this protein, motor neurons degenerate and nerve impulses are not carried between the brain and muscles, resulting in characteristic muscle weakness and impaired movement (*Bodamer 2020, Finkel et al 2018, Genetics Home Reference 2020*).
- There is also a modifying (or “backup”) gene called *SMN2*, which generates a smaller amount of functional SMN protein. The number of *SMN2* gene copies varies among individuals, and patients with a higher number of *SMN2* gene copies tend to have a less severe SMA type (*Bodamer 2020, Calucho et al 2018*).
- There are several forms of SMA with varying degrees of severity and ages of onset (*Bodamer 2020, Genetics Home Reference 2020, Glascock et al 2018, Rao et al 2018*).
- In SMA type 1, untreated patients have severe weakness and hypotonia and never gain the ability to sit unsupported. Patients with SMA type 1 typically have an onset of symptoms between the age of 0 and 6 months, and have a typical lifespan of < 2 years without permanent ventilation.
- Patients with SMA type 2 (intermediate), 3 (mild), or 4 (adult-onset) experience a later onset and less severe symptoms usually characterized by varying degrees of muscle weakness. Type 0 (prenatal) is the rarest and most severe form, with newborns typically living for < 6 months.
- SMA type 1 is the most common form, affecting approximately 58% of patients. Type 2 and type 3 occur in approximately 29% and 13% of patients, respectively, and type 4 is less common (< 5%) (*Food and Drug Administration [FDA] medical review 2016*). Mothers may notice a decrease of fetal movement in late pregnancy, and some experts classify prenatal onset as type 0 SMA, which is very rare (*Bodamer 2020, FDA medical review 2016*).
- Management of SMA has historically been limited to supportive measures, focusing on providing nutrition and respiratory assistance and preventing or treating the complications of weakness. Nonpharmacologic treatments include physical therapy, spinal bracing, chest physiotherapy, and respiratory support (*Bodamer 2020, Finkel et al 2018, Mercuri et al 2018[a]*).
- In December 2016, Spinraza (nusinersen) became the first FDA-approved product for the treatment of SMA. The FDA granted nusinersen Fast Track designation, Orphan Drug designation, and Priority Review (*FDA 2016*).
- Nusinersen is an antisense oligonucleotide designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Nusinersen binds to sites within *SMN2* pre-mRNA, promoting inclusion of exon 7 in *SMN2* mRNA transcripts and increasing production of full-length, functional SMN protein (*Finkel et al 2016*).
- Zolgensma (onasemnogene abeparvovec-xioi; referred to as onasemnogene abeparvovec), approved by the FDA in May 2019, is the second FDA-approved product for the treatment of SMA. Onasemnogene abeparvovec was granted Priority Review by the FDA, and received Breakthrough Therapy, Fast Track, and Orphan Drug designations (*FDA 2019*).
- Onasemnogene abeparvovec is a gene therapy that uses a viral vector to deliver a copy of the gene encoding the human SMN protein. The virus enters the nucleus of neurons and forms an episome (a DNA molecule that replicates independently of chromosomal DNA). The episome is transcribed and translated to produce the missing SMN protein.
- Evrysdi (risdiplam), approved by the FDA in August 2020, is the third FDA-approved product for the treatment of SMA. Risdiplam was granted Priority Review by the FDA, and received Fast Track and Orphan Drug designations.
- Risdiplam is a splicing modifier that increases exon 7 inclusion in the *SMN2* mRNA transcripts, thereby increasing production of full-length SMN protein (*Evrysdi prescribing information 2020*).

- Medispan class: Spinal Muscular Atrophy Agents
- Medispan class: Spinal Muscular Atrophy – Gene Therapy Agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Evrysdi (risdiplam)	-
Spinraza (nusinersen)	-
Zolgensma (onasemnogene abeparvovec-xioi)	-

(Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Evrysdi (risdiplam)	Spinraza (nusinersen)	Zolgensma (onasemnogene abeparvovec-xioi)
Treatment of SMA in patients 2 months of age and older	✓		
Treatment of SMA in pediatric and adult patients		✓	
Treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the <i>SMN1</i> gene			✓ *

* Limitations of use: The safety and effectiveness of repeat administration of onasemnogene abeparvovec have not been evaluated. The use of onasemnogene abeparvovec in patients with advanced SMA (eg, complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Zolgensma (onasemnogene abeparvovec-xioi)

- The safety and efficacy of onasemnogene abeparvovec were evaluated in 3 clinical trials, START, STR1VE and SPR1NT.
 - START was a phase 1, open-label trial of 15 patients with SMA type 1 who had 2 copies of *SMN2*. Two cohorts were treated: 3 patients in cohort 1 received a low dose of Zolgensma, while 12 patients in cohort 2 received a high dose of Zolgensma. After 24 months of treatment, all patients in cohort 2 were alive and none required permanent ventilation (described as ≥ 16 hours per day of required ventilatory support for 14 consecutive days in the absence of acute reversible illness or perioperative change). One patient in group 1 reached a pulmonary event at 28.8 months of age. Patients also had improvement in meeting certain motor milestones, with the majority gaining the ability to sit unassisted, roll over, and achieve head control. Gains in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) were also noted (*Al-Zaidy et al 2019, Mendell et al 2017*).
 - Ten of the 12 patients in cohort 2 enrolled in the START long-term follow-up (LTFU) study. As of December 31, 2019, all 10 patients were alive and free of permanent ventilation, no previously-achieved motor milestone had been lost, and 2 patients gained a new milestone of standing with assistance. There were no new treatment-related serious adverse effects (AEs) and no AEs of special interest during the LTFU study. Some of the patients in the LTFU study have received subsequent therapy with nusinersen (*Novartis 2020[a]*).
 - STR1VE was an open-label, single-arm, multicenter trial in the U.S that evaluated the safety and efficacy of Zolgensma in patients with SMA type 1 who were < 6 months of age at the time of gene therapy, with 1 or 2 copies of *SMN2* and who had bi-allelic *SMN1* gene deletion or point mutations.
 - Data as of March 8, 2019 (median duration of follow-up, 10.2 months) showed that of 20 patients who reached 10.5 months of age or discontinued the study prior to 10.5 months of age, 19 (95%) were surviving without permanent

ventilation. Of 15 patients who had reached 13.6 months of age or discontinued prior to 13.6 months, 13 (87%) were surviving without permanent ventilation (*Day et al 2019*).

- According to updated data provided by the manufacturer in March 2020, 20 of 22 patients (91%) met the co-primary endpoint of event-free survival at 14 months, and 13 of 22 patients (59%) met the co-primary endpoint of functional sitting for ≥ 30 seconds at 18 months of age. Sustained improvements in CHOP-INTEND scores were also noted (*Novartis 2020[a]*).
- SPR1NT is an ongoing, Phase 3, open-label, single-arm, multicenter trial designed to evaluate the safety and efficacy of Zolgensma in pre-symptomatic patients with SMA and 2 or 3 copies of *SMN2* who were ≤ 6 weeks of age. The primary outcome measure for patients with 2 copies of *SMN2* is independent sitting for ≥ 30 seconds by 18 months. The primary outcome measure for patients with 3 copies of *SMN2* is standing without support for at least 3 seconds by 24 months (*Avexis 2019, Strauss et al 2019*).
 - As of December 31, 2019, 14 patients with 2 copies of *SMN2* and 15 patients with 3 copies of *SMN2* had been treated. In the 2-copy cohort, 8 patients so far were able to sit independently for ≥ 30 seconds (range, 5.7 to 11.8 months of age), and 4 patients were able to walk independently. Of the patients with 3 copies of *SMN2*, 4 patients were able to stand alone without support for ≥ 3 seconds (9.5 to 12.4 months of age) and 3 patients were able to walk independently (12.2 to 15.1 months of age). Patients in both cohorts who had not achieved these milestones yet were still within the normal age development window for these milestones (*Novartis 2020[a]*).
- Zolgensma is still being studied in a number of trials in pursuit of expanding patient populations. Of note, the STRONG trial is a Phase 1 trial investigating intrathecal delivery in children with SMA type 2 aged 6 months to 5 years (*Clinicaltrials.gov 2020*). Based on their review of data from STRONG, the FDA has notified the manufacturer that they recommend a pivotal confirmatory study to supplement the STRONG data in order to support a regulatory submission for intrathecal use (*Novartis 2020[b]*).

Spinraza (nusinersen)

- Key clinical trials supporting the safety and efficacy of nusinersen include ENDEAR, CHERISH, and NURTURE.
 - The pivotal trial ENDEAR (N = 121) was a 13-month, Phase 3, randomized, sham-controlled, double-blind, multicenter trial in patients 7 months or younger who had an onset of SMA symptoms at ≤ 6 months of age and had homozygous deletion or mutation of *SMN1* and 2 copies of the *SMN2* gene (*Finkel et al 2017*).
 - At interim analysis, a higher proportion of patients treated with nusinersen had a motor milestone response than those in the control group (41% vs 0%, $p < 0.001$), prompting early termination of the trial. The final analysis showed that 51% of the nusinersen-treated group had a motor milestone response, compared with no patients in the control group. Motor milestones reached included achievement of full head control (22%), ability to roll over (10%), ability to sit independently (8%), and ability to stand (1%).
 - A co-primary endpoint of event-free survival also favored nusinersen vs placebo (61% vs 32%; $p = 0.005$).
 - Patients in the nusinersen group also had a 63% lower risk of death compared with the control group (hazard ratio, 0.37; 95% confidence interval [CI], 0.18 to 0.77; $p = 0.004$).
 - CHERISH (N = 126) was a Phase 3, randomized, sham-controlled, double-blind, multicenter trial in patients aged 2 to 12 years with later-onset SMA. The primary endpoint was the least-squares mean change from baseline in the Hammersmith Functional Motor Scale-Expanded (HFMSE) score at 15 months of treatment (*Mercuri 2018[b]*).
 - In the pre-planned interim analysis, there was a significant improvement in the HFMSE from baseline to 15 months in the nusinersen group vs the control group (mean difference in change, 5.9 points; 95% CI, 3.7 to 8.1; $p < 0.001$).
 - Results of the final analysis were consistent with results of the interim analysis. In the final analysis, 57% of the children in the nusinersen group vs 26% in the control group had an increase from baseline to month 15 in the HFMSE score of at least 3 points ($p < 0.001$), and the overall incidence of AEs was similar in the nusinersen group and the control group (93% vs 100%, respectively).
 - The NURTURE study is an ongoing, Phase 2, open-label, single-arm trial to evaluate the use of nusinersen in patients with SMA and 2 or 3 copies of *SMN2* who were ≤ 6 weeks of age and asymptomatic at the time of treatment initiation. The primary endpoint was time to death or respiratory intervention (invasive or non-invasive for ≥ 6 hours per day continuously for ≥ 7 days or tracheostomy). At an interim analysis published in 2019, 25 patients had been enrolled, of whom 15 had 2 *SMN2* copies and 10 had 3 *SMN2* copies. At the time of the interim analysis, 4 participants (16%) had utilized a respiratory intervention. All patients were alive and none required permanent ventilation. Efficacy was further supported by the achievement of motor milestones by HINE-2 and motor function by CHOP-INTEND. Of note, all patients achieved the milestone of “sitting without support” and 23 of 25 patients (92%) achieved “walking with assistance” (*De Vivo et al 2019*).

- In June 2020, the manufacturer reported updated data noting that all children treated pre-symptomatically were alive and none required permanent ventilation after up to 4.8 years of continuous treatment. In addition, patients continued to maintain and make progressive gains in motor function. The study has been extended by an additional 3 years to allow the collection of continued data (*Biogen 2020*).
- The FDA-approved indication for nusinersen does not limit its use to certain ages or SMA types. The FDA medical review noted that the underlying cause of SMA (a shortage of SMN protein) is common to patients with all SMA types, and it is reasonable to expect that nusinersen should provide clinical benefits in all SMA types. Open-label studies included patients 2 to 17 years of age with 2 to 5 *SMN2* copies and symptom onset corresponding to types 2 and 3 SMA; these results plus the initial summary of the sham-controlled trial in later-onset patients support the conclusion that nusinersen provides clinical benefits to patients with types 2 and 3 SMA and allow reasonable extrapolation to these populations. Given the invasive nature of nusinersen administration, patients with milder forms of SMA (type 4) may need to weigh potential benefits, risks and discomfort, and relative symptom severity to make individual treatment decisions (*FDA medical review 2016*).

Evrysdi (risdiplam)

- Evidence for the safety and efficacy of risdiplam is available from results of 2 clinical trials, FIREFISH and SUNFISH. Both studies are still ongoing.
 - FIREFISH is a 2-part, Phase 2/3, open-label, multicenter, dose-escalation study assessing the safety and tolerability of risdiplam in infantile-onset SMA type 1 patients aged 1 to 7 months.
 - In part 1, 21 infants were assigned to group A (n = 4) receiving a low dose or group B (n = 17) receiving a high dose that was adjusted up to the recommended dose of 0.2 mg/kg/day. Of the infants who were treated with the recommended dosage of risdiplam 0.2 mg/kg/day, 7 of 17 (41%) were able to sit independently for ≥ 5 seconds as assessed by the Bayley Scales of Infant and Toddler development Third Edition (BSID-III) after 12 months of treatment, a milestone beyond that expected in the natural history of the disease. Additionally, 90% of patients (19/21) were alive without permanent ventilation (and reached 15 months of age or older) (*Evrysdi prescribing information 2020*). The most common AEs included pyrexia, upper respiratory tract infections, rash, diarrhea, vomiting, pneumonia and constipation (*Evrysdi AMCP Dossier 2020*).
 - The manufacturer announced 2-year data for FIREFISH part 1, noting that an estimated 88% of patients were alive and required no permanent ventilation after 2 years. Patients continued to achieve motor milestones, including 59% (10/17) sitting without support for ≥ 5 seconds, 65% (11/17) maintaining upright head control, 29% (5/17) turning over, and 30% (5/17) standing either supporting weight or with support. No new safety signals were identified (*Genentech 2020*).
 - Part 2 is a pivotal single-arm study evaluating the use of risdiplam in 41 infants with SMA type 1 for 24 months. Infants received risdiplam at a dose of 5 mg once daily for patients with a body weight ≥ 20 kg or 0.25 mg/kg for patients with a body weight < 20 kg. The primary outcome is the proportion of infants sitting without support for ≥ 5 seconds after 12 months on treatment as assessed by BSID-III. A primary analysis at 12 months (November 2019) showed that 12/41 infants (29%; 90% CI, 17.8% to 43.1%) were sitting without support for ≥ 5 seconds. After 24 months in part 2, infants will continue in an open-label extension phase (*Evrysdi AMCP Dossier 2020*).
 - SUNFISH is a 2-part, double-blind, placebo-controlled trial in children and young adults aged 2 to 25 years old with SMA type 2 and 3 (*Evrysdi AMCP Dossier 2020*).
 - Part 1 (N = 51) was a dose-finding phase evaluating safety and tolerability of risdiplam. Patients received risdiplam or placebo for a minimum of 12 weeks, followed by open-label use of risdiplam at the dose selected for Part 2. Exploratory results at 12 months showed improvements in motor function compared to natural history.
 - In Part 2, 180 patients were randomized (type 2, 71%; type 3, 29%) to risdiplam or placebo for 24 months followed by an open-label extension period. The primary endpoint was the change from baseline in motor function measure 32 scale (MFM-32) at month 12; the average baseline MFM-32 score was 45 in the risdiplam group vs 47 in the placebo group. The primary analysis showed a statistically significant 1.36-point increase from baseline MFM-32 score in the risdiplam group (95% CI, 0.61 to 2.11) compared to a -0.19-point change in the placebo group (95% CI, -1.22 to 0.84). The most common AEs that occurred in > 10% of risdiplam-treated patients and more commonly than with placebo were fever, diarrhea, and headache. The most common serious AE in the risdiplam arm was pneumonia in 9 patients. There was a trend for more grade 3 to 4 AEs in the risdiplam group.
- Additional studies of risdiplam are ongoing (*Evrysdi AMCP Dossier 2020*). JEWELFISH is a Phase 2, open-label, exploratory study investigating the safety, pharmacokinetics, and pharmacodynamics of risdiplam in 174 patients 6

months to 60 years of age with SMA who had previously been treated with nusinersen, onasemnogene abeparvovec, or certain other investigational SMA therapies. RAINBOWFISH, which is currently enrolling patients, is a Phase 2, open-label study evaluating the use of risdiplam in pre-symptomatic SMA patients up to 6 weeks of age at the time of treatment initiation.

Other studies

- A recent observational cohort study showed benefit of nusinersen for adults aged 16 to 65 years with SMA. A clinically meaningful improvement (defined as an increase of 3 points or more in the HFMSE score compared to baseline) was observed with nusinersen treatment at 6 months in 35 of 124 patients (28%), at 10 months in 33 of 92 patients (36%), and at 14 months in 23 of 57 patients (40%) (*Hagenacker 2020*).
- A Cochrane review of 2 randomized controlled trials assessed the safety and efficacy of drug therapies (nusinersen and riluzole) designed to slow or stop the progression of SMA type 1. Riluzole is not indicated for the treatment of SMA. Authors concluded that intrathecal nusinersen probably prolongs ventilation-free and overall survival in infants with SMA type 1. Additionally, a greater proportion of infants treated with nusinersen achieved motor milestones. In the riluzole trial, 3 of 7 children treated with riluzole were still alive at the ages of 30, 48, and 64 months, whereas all 3 children in the placebo group died. None of the children in the riluzole or placebo group developed the ability to sit, which was the only milestone reported in the study (*Wadman et al 2019*).
- A Cochrane review of 14 randomized controlled trials evaluated the efficacy of various drug treatments, most of which are not indicated for the treatment of SMA, to slow the disease progression of SMA types 2 and 3. The trials evaluated gabapentin, hydroxyurea, nusinersen, olesoxime, phenylbutyrate, somatropin, thyrotropin-releasing hormone, valproic acid, and combination valproic acid/acyl-L-carnitine. Treatment varied from 3 to 24 months. Overall, no treatment showed a clinically important effect on motor function in SMA types 2 or 3, except for intrathecal nusinersen, which showed a 3.7-point improvement in motor function in children with SMA type 2 based on the HFMSE scale with moderate quality evidence (*Wadman et al 2020*).

CLINICAL GUIDELINES

- **SMA Newborn Screening Working Group.** Treatment algorithm for infants diagnosed with SMA through newborn screening (*Glascock et al 2018*)
 - Clinical and preclinical data indicate that early treatment will be critical in order to modulate the rapid, progressive degeneration seen in SMA, particularly SMA type 1. Animal studies also show that the best results occur when drugs are given as early as possible.
 - Recommendations for the use of SMN-upregulating treatment for patients with a confirmed positive result for SMA on newborn screening are based on the number of *SMN2* copies, as follows:
 - 1 *SMN2* copy: probable SMA type 0. Treatment is recommended if the patient is truly pre-symptomatic. If symptoms are present, physician discretion is recommended. (Most patients with 1 copy of *SMN2* will be symptomatic at birth.)
 - 2 *SMN2* copies: probable SMA type 1. Treatment is recommended.
 - 3 *SMN2* copies: probable SMA type 2 or type 3. Treatment is recommended.
 - ≥ 4 *SMN2* copies: probable SMA type 3 or type 4. Waiting to treat is recommended; patients should be monitored and treated upon the onset of symptoms. (The committee was divided on this recommendation.)
 - In patients with ≥ 4 copies of *SMN2*, who are not immediately treated with a disease-modifying therapy for SMA, the following key recommendations are made:
 - Infants identified as having ≥ 4 *SMN2* copies should be referred to someone who can identify their exact copy number (some commercial laboratories report the result only as " ≥ 4 ").
 - Routine follow-up care should ideally occur every 3 to 6 months until the patient reaches 2 years of age, and every 6 to 12 months thereafter. This would ensure the detection of very rare cases in which children with ≥ 4 *SMN2* copies have SMA type 1 or 2.
 - Certain follow-up assessments recommended include electromyography (EMG), compound muscle action potential (CMAP), myometry, physical examinations, and motor function scales.
 - The working group acknowledges that the future availability of new FDA-approved therapies will prompt the need for additional consideration by physicians and patients, as each drug will present unique benefits, risks, and burdens.

- **SMA Care Group.** Diagnosis and management of SMA. Part 1: recommendations for diagnosis, rehabilitation, orthopedic, and nutritional care (*Mercuri et al 2018[a]*) and Part 2: pulmonary and acute care; medications, supplements, and immunizations; other organ systems; and ethics (*Finkel et al 2018*). The following recommendations outline aspects associated with supportive pharmacological care:
 - Over the last decade, the approach to treating the pulmonary manifestations of SMA has become more proactive, with introduction of therapies earlier in the disease process. Respiratory support should be the highest priority.
 - Management may include airway clearance, noninvasive positive pressure ventilation, and tracheotomy ventilation in select patients. Continuous positive airway pressure (CPAP) should not be used routinely.
- **European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy** (*Kirschner et al 2020*). With the recent approval of Zolgensma, many patients could be eligible for the gene therapy with the broadly defined approved indication. However, clinical trials studied very specific patient groups for gene therapy (eg, SMA type, age and weight), thus individual treatment decisions should be made on a case-by-case basis. The statement of 11 points highlights 3 areas including selection criteria, structural requirements for administration, and generation of additional evidence. Key points are as follows:
 - **Selection criteria:**
 - Traditional SMA types (0 to 4) alone are not enough to define patients who would most benefit from gene therapy. Age at onset, disease duration, and motor function status are key factors that predict response to treatment in symptomatic patients, whereas treatment decisions for presymptomatic patients should primarily be based on *SMN2* copy number. Although the approval of Zolgensma is based on clinical trials in patients ≤ 6 months old weighing less than 8.4 kg, it is indicated in patients up to 2 years old. However, little is known about the safety and efficacy in older and heavier patients; in these cases nusinersen is available as a treatment option. When administered after the age of 6 months and/or in advanced stages of the disease, caregivers should be made aware that there are no published data on efficacy and safety. It is important for physicians to discuss the benefit/risk ratio and to carefully manage parents' or patients' expectations.
 - In patients presenting with severe symptomatic disease, there is a high risk of living with severe disability despite the use of gene therapy. Palliative care is recommended as an alternative treatment option in these patients.
 - There is no evidence that combination therapy (eg, Zolgensma plus nusinersen) is superior to any single treatment alone. Before more evidence is available, combination of both approved therapies should not be part of routine care.
 - **Structural requirements for administration:** Providers performing gene therapy should have broad expertise in the assessment and treatment of SMA according to international standards. The ideal time between diagnosis and initiation of a disease modifying treatment should be no longer than 14 days. This is particularly important in infants due to the progressive nature of the disease.
 - **Generation of additional evidence:** Data regarding safety and effectiveness should be collected for all treated patients. Institutions using Zolgensma should be adequately equipped with resources to safely administer the therapy and provide care and long-term monitoring. The statement suggests that patients weighing ≥ 13.5 kg may be best treated with Zolgensma in a clinical trial setting only.

SAFETY SUMMARY

- **Contraindications**
 - Evrysdi: none
 - Spinraza: none
 - Zolgensma: none
- **Boxed Warning**
 - Evrysdi: none
 - Spinraza: None
 - Zolgensma: acute serious liver injury, elevated aminotransferases; higher risk in patients with pre-existing liver impairment
- **Warnings and precautions**
 - Evrysdi: none
 - Spinraza: thrombocytopenia, coagulation abnormalities, renal toxicity
 - Zolgensma: thrombocytopenia, elevated troponin

- AEs
 - Evrysdi:
 - Common AEs in infantile-onset SMA ($\geq 10\%$): upper respiratory tract infection, pneumonia, constipation, vomiting, fever, diarrhea, and rash
 - Common AEs in later-onset SMA ($\geq 10\%$): fever, diarrhea, and rash
 - Spinraza:
 - The most common AEs ($\geq 20\%$ of Spinraza-treated patients and occurred at least 5% more frequently vs placebo-treated patients) include:
 - Infantile-onset SMA: lower respiratory infection and constipation
 - Later-onset SMA: pyrexia, headache, vomiting, and back pain
 - Zolgensma
 - The most common AEs ($\geq 5\%$) include: elevated aminotransferases and vomiting
- Use in specific populations:
 - Spinraza and Evrysdi, Pregnancy: may cause fetal harm (based on animal data).
 - Evrysdi, Hepatic impairment: Use should be avoided in patients with hepatic impairment.
 - Zolgensma, Pediatric use: Use in premature neonates before reaching full term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Evrysdi (risdiplam)	Powder for reconstitution (oral solution)	Oral	Once daily	Administer dose after a meal using the provided oral syringe.
Spinraza (nusinersen)	Injection	Intrathecal	4 loading doses: first 3 doses at 14-day intervals, 4 th dose 30 days after the 3 rd Maintenance dose every 4 months thereafter	To be given by, or under the direction of, healthcare professionals experienced in performing lumbar punctures; administered as an intrathecal bolus over 1 to 3 minutes; sedation should be considered as indicated by the clinical condition of the patient; ultrasound or other imaging techniques should be considered to guide administration, particularly in younger patients.
Zolgensma (onasemnogene abeparvovec-xioi)	Injection	IV	One-time administration; 1.1×10^{14} vector genomes (vg)/kg	Administered over 60 minutes using a syringe pump. There are a total of 22 kit configurations, consisting of 2 to 9 vials (5.5 mL and/or 8.3 mL), to treat patients weighing 2.6 to 13.5 kg.

See the current prescribing information for full details

- Zolgensma: vials are shipped frozen and are stable under refrigeration for 14 days after receipt.

CONCLUSION

- SMA is a serious neuromuscular disease characterized by degeneration of motor neurons in the spinal cord and brainstem. Clinical features include progressive muscular atrophy and weakness.
 - SMA is caused by an inherited genetic mutation affecting the *SMN1* gene, causing a deficiency of the critical SMN protein.
 - Several subtypes of SMA exist, with varying severity and ages of onset.

- Zolgensma has the potential to significantly improve the disease course of SMA with a 1-time IV dose. Published efficacy data are limited to approximately 15 patients, all of whom had SMA type 1 and 2 copies of a modifying gene, *SMN2*.
 - Zolgensma is a gene therapy that uses a viral vector to deliver a copy of the gene encoding the human SMN protein.
 - The main safety risks include elevated transaminases and potential acute serious liver injury.
- Nusinersen has demonstrated efficacy in patients with SMA types 1, 2, and 3 and in pre-symptomatic patients; however, nusinersen requires intrathecal dosing several times per year throughout the patient's lifetime.
- In pivotal trials, risdiplam improved motor function in people living with SMA over a large range of ages and levels of disease severity including types 1, 2, and 3.
 - Risdiplam helped infants survive longer without the need for permanent ventilation and sit without support for ≥ 5 seconds, a key motor milestone not normally seen in the natural course of the disease.
 - Risdiplam is an oral medication that is administered by the patient/caregiver, compared to intrathecal (nusinersen) and IV (Zolgensma) which require a healthcare professional.
- The specific place in therapy for each SMA agent, including the potential role for sequential treatment, requires further study.

APPENDIX

- **Bayley Scales of Infant and Toddler development Third Edition (BSID-III)** (*Evrydsi dossier 2020*)
 - BSID-III is intended for children age 1 to 42 months. The assessment is completed over 30 to 90 minutes and measures 5 developmental domains: adaptive behavior, cognition, language, motor, and social-emotional. Raw scores of each successfully completed item are converted to subtest scaled scores and to a composite standard score. The scores determine the child's performance compared with typically developing children of their age. While it is not a disease-specific measure, the BSID-III has high reliability and validity.
- **Hammersmith Functional Motor Scale – Expanded (HFMSE)** (*Spinraza dossier 2016*)
 - Expanded version of the original 20-item Hammersmith Functional Motor Scale that incorporates 13 items from the Gross Motor Function Measure assessment.
 - Consists of 33 items evaluating the child's ability to perform activities. Each item is scored on a 3-point scale, with a score of 2 for "performs without modification," 1 for "performs with modification/adaptation," and 0 for "unable to perform."
 - The total score can range from 0 (all activities failed) to 66 (all activities achieved).
 - A clinically meaningful change has been estimated to be a 3-point change at 6 months.
- **Hammersmith Infant Neurological Examination (HINE)** (*De Sanctis 2016, Spinraza dossier 2016, FDA Medical Review 2016, Together in SMA 2016*)
 - Measures functional ability and achievement of motor milestones.
 - Contains 26 items; total possible score is 78. Healthy-term infants should have a median score ≥ 67 at 3 months and ≥ 70 at 6 months. At 9 or 12 months, scores ≥ 73 are regarded as optimal.
 - Section 1 is based on the neurological exam (postures, cranial nerve function, reflexes, tone, and movements).
 - Section 2 (HINE-2) evaluates development of motor function based on 8 items (head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling, standing, and walking); each item is scored between 0 and 2 to 4, for a maximum score of 26.
 - Section 3 evaluates the state of behavior (consciousness, social orientation, and emotional state).
- **Motor Function Measure 32 (MFM-32)** (*Evrydsi dossier 2020*)
 - MFM-32 is typically used in people older than 6 years; however it has been validated in children as young as 2 years old. The assessment typically takes around 30 to 40 minutes to complete. Each item of the MFM is scored using a 4-point Likert scale, ranging from 0 to 3, based on the subject's maximal abilities without assistance. The scores on each of the 32 items are summed and converted to a 0 to 100 total score; the lower the total score, the more severe the impairment.
- **Upper Limb Module (ULM)** (*Spinraza dossier 2016*)
 - Designed to assess upper limb functional abilities in patients with SMA, including young children and patients with severe contractures in the lower limbs.
 - Consists of 9 upper limb performance items that reflect activities of daily living.
 - The total score ranges from 0 to 18 points, with higher scores indicating greater functional abilities.
 - An increase of ≥ 2 points is considered clinically meaningful.

- A revised version of the ULM consists of 20 upper limb performance items.

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