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UPDATED OVERVIEW OF DRUGS WITH APPROVED ORPHAN INDICATIONS: WITH FOCUS ON SPINRAZA

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Introduction

An estimated 25 million Americans suffer from a rare or "orphan" disease, defined as one that affects fewer than 200 thousand people across the United States (US).[1,2] There are approximately 7,000 known rare diseases, of which fewer than 5% have developed treatments.[1] Today, biotechnology and pharmaceutical companies, small and large, are filling this treatment vacancy at an accelerated pace.[3,4] The 1983 Orphan Drug Act (ODA) was enacted to spur meaningful advancements for persons with rare diseases by providing tax break and other marketing incentives to companies that brought "orphan drugs" (i.e., drugs that have indications for orphan diseases) to the market. It was perceived that a drug company would not otherwise be motivated to develop products in the rare-disease arena because research expenditures would not be recouped, much less a profit realized.[5,6]

Although a drug may be approved for a rare disease, its use may actually become widespread. Some factors that increase orphan-drug utilization include situations when (1) the orphan-approved drug also has non-orphan indications (e.g. Humira, Crestor), and/or (2) the orphan-approved drug has multiple approved orphan-designations or off-label supported uses (e.g. Gleevec).

The increase of orphan-drug approvals has challenged health-plan designers. Orphan-related approvals are beginning to rival non-orphan-drug approval rates. In 2017, 39% of the novel medications brought to market were approved for an orphan indication.[7,8]

EvaluatePharma, a company that analyzes financial markets, projects continued growth for the share of sales from orphan-drugs (among the total worldwide prescription-drug sales).[3,9] They estimated the 2016 US average cost per patient per year for orphan drug use was $140,443 compared to $27,756 for non-orphan drugs.[3] Developing prescribing criteria to help ensure the appropriate patients receive these medications (according to labeled approved indications, guideline recommendations, or clinical trial criteria) may help minimize misuse/inappropriate use.

This report provides an updated overview of the orphan drug landscape including Medicaid utilization data for selected injectable products with orphan-designation approvals. The previous DUR report (December 2017), *"Overview of Drugs with Approved Orphan Indications: with Focus on Carbaglu*," provided utilization data for orally, intramuscularly, and subcutaneously administered products. This report presents utilization data for other injectable orphan products not captured in the previous report. More detailed information will be provided for nusinersen (Spinraza; Biogen, Inc. Cambridge, MA), indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

Methodology

We searched PubMed, Cochrane Central, and websites for the US Food and Drug Administration (FDA), the National Organization for Rare Disorders, Orpha.net, and the American Cancer Society for background information on orphan-drugs and for specific information related to nusinersen and the management of spinal muscular atrophy. Additional drug information resources, such as Lexicomp, Micromedex, and the FDA Orange Book were also used.

Data Sources

Master orphan drug list— A list of orphan-drug approvals from 1983 through December 2017 was obtained from the website of the FDA's 'Search Orphan Drug Designations and Approvals' database: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/. Since this list represents each orphan-approval for a drug, many of which have more than one approved indication, it was then duplicated to create a clean list of products to use for utilization queries. This list was narrowed to brand name products administered by injectable routes, with discontinued products removed. The route-of-administration detail for this selection process was derived individually for each product using drug information resources (Micromedex and Lexicomp). Appendix B provides a list of the queried products. The DUR report (December 2017), *"Overview of Drugs with Approved Orphan Indications: with Focus on Carbaglu*," provided utilization data for oral (PO), intramuscular (IM), and subcutaneous (SQ) product formulations.

Drug utilization extraction— Medicaid references 412,310 distinct NDCs (national drug codes) in the database. An asymmetric spelling distance linkage algorithm was used to match product information maintained by Medicaid against the derived list of trade names identified as orphan drugs of interest in this review (see Appendix B for list). Using conservative matching algorithm parameters in order to maximize the number of relevant drugs captured, 2,734 possible orphan-drug matching NDCs were obtained. After a manual review for matching accuracy and defined administering routes, 1,244 NDCs were identified for review. There are 10,682 Medicaid records, from pharmacy and medical claims, from January 2017 to January 12th, 2018 that referenced NDCs from the finalized list.

Search Results

I. Orphan Drugs

The Orphan Drug Designation Program (ODDP), overseen by the FDA's Office of Orphan Products Development, requires either that the orphan-designated product treat a rare disease affecting less than 200,000 Americans or that the manufacturer convincingly show it will not recoup developmental costs from sales within the US.[10] Incentives for orphan-drug development include a tax discount (50% tax credit on certain research/development costs[11]), an application fee waiver, grant availability, 7 year marketing exclusivity, and research design assistance. Additionally, there is flexibility in what the FDA considers to be substantial evidence for demonstrating the drug's safety and efficacy profile.[6,12,13]

From 2013 through 2017, an average of 49 orphan-designated drug approvals per year were granted by the FDA.[7] This is a dramatic increase compared to pre-1983 when there were fewer than 10 orphan-related products that entered the market between 1973 and 1983.[5] The number of orphan-drug designation requests submitted by companies continues to grow.[14] In recent years this rate has overwhelmed the capacity of FDA review boards. The pace of orphan reviews will quicken with the implementation of the 2017 Orphan Drug Modernization Plan, which should enable the FDA to finish reviewing a significant backlog of applications. The FDA commissioner plans to address certain loopholes, especially those involving small affected pediatric subpopulations of a common adult disease state for which a drug company may seek a pediatric orphan designation to avoid the Pediatric Research Equity Act requirements.[14]

Prior to performing a pivotal clinical trial, manufacturers must detail the natural history of the rare condition (e.g. disease manifestations, variability in the course and possible subtypes of the disease) and propose trial design and endpoints to the FDA. The challenge of small patient populations has stemmed a case-by-case evidence consideration approach by the FDA.[13,15] Evidence from small trial populations and retrospective data from case reports may be considered.[16,17]

If broad approval is granted for a drug where robust data addresses only limited subgroups, payer uncertainty may arise concerning the value of the drug for those subgroups where data isn't fully elucidated. Dr. Prasad, M.D. MPH.* highlights this matter, as he describes the paradox of lofty medication costs for agents that are often non-curative, with significant yet small or even unclear benefits for certain populations: [18,19]

> "*Irrespective of cost, a fundamental principle of evidence-based medicine—caution in extrapolating benefits shown in severe disease settings to more indolent settings— may form the basis for denial of coverage*…"[19]

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* *"Vinay K. Prasad MD MPH is a hematologist-oncologist and Assistant Professor of Medicine at the Oregon Health and Sciences University. He also holds appointments in the Division of Public Health and Preventive Medicine, and as a Senior Scholar in the Center for Health Care Ethics."*[18] He has published research on oncology drugs, health policy, evidence-based medicine, bias, public health, and preventive medicine.

> "*Although some may view drugs with marginal results as a path of incremental progress, the approval of these agents often directly competes against ongoing clinical trials, and may paradoxically slow progress if they are used instead of accrual toward trials.*"[19]

There are several concerns regarding a price premium for orphan-drug products. In some instances it is theorized that a manufacturer may set the drug price to reflect the "from-scratch" developmental value for an orphan-only indication despite the product being previously approved for more common, high-demand indications. Even if not used for a common indication, orphan-drugs may still provide massive profits to manufacturers despite being used for small patient populations.[3,20,21] Aligning drug pricing with the degree of benefit a medication provides is a complex task. Nonetheless, it appears that sponsors, with monopoly position, are able to decide this independently. Table 1 summarizes some concerns related to the orphan-drug marketing landscape.

Table 1. Different viewpoints related to the marketing of orphan-drug products[3,20-26]

Costs to Insurer and Beneficiaries		
• Orphan related drugs costs are perceived as driving up overall healthcare costs • "*There are indications drug companies pursue prices towards the upper limit of the "willingness to pay". Many purchasers (governments, health insurers, etc…) are not really armed to set limits to these prices, nor to set reasonable boundaries to the willingness to pay*."[26]	*versus*	• Drug costs and medical care costs in general go up over time

• A small targeted population allows a price premium for orphan drugs;[3] however there is concern when profits become a windfall
  ▪ Blockbuster sales: some propose that orphan status should be eliminated for a designated drug if sales meet a certain profit threshold
  ▪ The increasing average cost per beneficiary associated with the rapid growth rate in orphan drug sales may be unsustainable. Worldwide orphan-drug sales are expected to increase by 11% from 2017 to 2022 and account for 21% of all brand-name drug sales by 2022[3]
		• This price premium is justified by manufacturers as a means to recoup developmental costs and may attempt to reflect the rescue-of-life value for some advanced personalized drugs
		  ▪ Drug research and development is a long process, often leading to many failures before a success molecule is obtained
		  ▪ Drug use for non-orphan related indications may also contribute to profit

Concerns that a Drug Developer May Game the System		
• Salami slicing concept: breaking up a widespread disease state into narrow disease subtypes or age groups to accomplish low patient numbers to qualify for orphan status • Going around the Pediatric Research Equity Act by proposing orphan designation for a pediatric group when the drugs is approved for a non-orphan adult indication	*versus*	• Although a drug may be used widely for a common disease state, it still costs to perform research in a unique population or for a uniquely characterized disease for which the drug has not been studied in full

II. Descriptions of the Orphan Drug Subset

A. Table 2 provides a list of the novel orphan drugs approved in 2017; injectable medications are bolded and the table is ordered by most recent to oldest drug approval date. All products, with the exception of the biologics, are listed among the FDA's 2017 Novel Drug Approvals List.[8] Newly approved biologic products including axicabtagene ciloleucel, C1-esterase-inhibitor, tisagenlecleucel, and voretigene neparvovec-rzyl are listed on the FDA's 2017 Biologic License Application Approval List.[27]

Table 2. Orphan drugs approved in 2017[7,8,27]

Generic Name	Trade Name (route of administration)	Approved Indication[a]	Marketing Approval Month in 2017
macimorelin acetate	Macrelin (PO)	For diagnosing adult growth hormone deficiency	December
voretigene neparvovec-rzyl	**Luxturna (Intraocular)**	Adeno-associated virus vector-based gene therapy for patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy with viable retinal cells	
emicizumab-kxwh	**Hemlibra (SQ)**	For prevention or reduction of bleeding frequency in adult and pediatric patients with hemophilia A	November
vestronidase alfa-vjbk	**Mepsevii (IV)**	For treatment of mucoploysaccharidosis type VII (MPS VII, Sly syndrome) in pediatric and adult patients	
letermovir	**Prevymis (IV)**	Prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT)	
acalabrutinib	Calquence (PO)	For adults with mantle cell lymphoma (MCL) who have received at least one prior therapy	October
axicabtagene ciloleucel	**Yescarta (IV)**	For adults with relapsed or refractory large B-cell lymphoma after ≥two lines of therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified	
copanlisib	**Aliqopa (IV)**	For adults with relapsed follicular lymphoma who have received at least two prior systemic therapies	September
tisagenlecleucel	**Kymriah (IV)**	For patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) refractory or in 2nd or later relapse	August
benznidazole	n/a (PO)	For children ages 2 to 12 years old with Chagas disease	
inotuzumab ozogamicin	**Besponsa (IV)**	For adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)	
enasidenib	Idhifa (PO)	For adults with relapsed or refractory acute myeloid leukemia with an isocitrate dehydrogenase-2 (IDH2) mutation	
C1-esterase-inhibitor	**Haegarda (SQ)**	For prevention of Hereditary Angioedema (HAE) attacks in adolescent and adult patients	June
edaravone	**Radicava (IV)**	Treatment of amyotrophic lateral sclerosis (ALS)	May
midostaurin	Rydapt (PO)	For adults with acute myeloid leukemia (AML) that is FLT3 mutation-positive, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation	April
brigatinib	Alunbrig (PO)	For patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib	

cerliponase alfa	**Brineura (Intraventricular)**	To slow the progression of loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency	
deutetrabenazine	Austedo (PO)	Treatment of chorea associated with Huntington's disease	
niraparib	Zejula (PO)	For maintenance of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy	March
avelumab	**Bavencio (IV)**	For adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma	
telotristat etiprate	Xermelo (PO)	Treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.	February
deflazacort	Emflaza (PO)	Treatment of Duchenne Muscular Dystrophy in patients 5 years of age and older	

Abbreviations: IM, intramuscular; IV, intravenous; PO, oral; SQ, subcutaneous

[a] Refer to professional prescribing information for the full indication and usage details for these products.

B. Roughly 200 unique brand name products have an orphan indication currently protected by the FDA's 7-year exclusivity period, with some having more than one orphan-indication.[7] Table 3 provides examples of injectable medications with 3 or more orphan indications that were approved for labeling since 2011 (still under 7-year exclusivity). These are currently only available as brand name products.[28]

Table 3. Examples of injectable drugs with ≥ 3 orphan-designation approvals since 2011[7]

Generic name (Brand name, route): # of orphan-designated approvals since 2011[a]
Adalimumab (Humira, SQ): 4
Bevacizumab (Avastin, IV): 6
Brentuximab vedotin (Adcetris, IV): 5
Canakinumab (Ilaris, SQ): 4
Daratumumab (Darzalex, IV): 3
Ipilimumab (Yervoy, IV): 3
Ofatumumab (Arzerra, IV): 3
Pembrolizumab (Keytruda, IV): 4
Nivolumab (Opdivo, IV): 5
Rituximab (Rituxan, IV): 3

Abbreviations: IV, intravenous; SQ, subcutaneous

[a] Several of these agents have received new approvals just within the last few months

- Of the products listed in Table 3, Utah Medicaid has developed prior authorization only for Avastin.[29] Humira is listed on the Utah Medicaid Preferred Drug List (PDL) as a preferred product.[30]

C. The 2017 report by EvaluatePharma summarized the following trends and predictions for the orphan-drug marketplace.[3]

i. The top 10 orphan drugs in the US for 2016, based on earnings, are shown in Table 4; the table is ordered by generic name and injectable agents are bolded.

Table 4. Top 10 selling US drugs with orphan indications in 2016 [3,7,31]

Generic name (Brand name), route	Rare disease for which an orphan approval remains protected by the 7 year marketing exclusivity term[7]	Other rare diseases for which the approval exclusion period has expired and other non-orphan indications
Bortezomib (Velcade), IV & SQ	• Mantle cell lymphoma first line	• Multiple myeloma (OI) • Mantle cell lymphoma second line (OI)
Cinacalcet (Sensipar), PO	• Severe hypercalcemia in primary hyperparathyroidism	• Hypercalcemia related to parathyroid carcinoma (OI) • Secondary hyperparathyroidism related to chronic kidney disease
Glatiramer acetate (Copaxone), SQ	• None	• Multiple sclerosis (OI)
Ibrutinib (Imbruvica), PO	• Chronic graft vs. host disease in adults • Marginal zone lymphoma: nodal, splenic, and extranodal • Small lymphocytic lymphoma • Chronic lymphocytic leukemia • Waldenstrom's macroglobulinemia • Mantle cell lymphoma	• None
Imatinib (Gleevec), PO	• Philadelphia+ acute lymphoblastic leukemia in pediatric patients	• Chronic myeloid leukemia (OI) • Aggressive systemic mastocytosis (OI) • Dermatofibrosarcoma protuberans (OI) • Gastrointestinal stromal tumors (OI) • Hypereosinophilic syndrome and/or chronic eosinophilic leukemia (OI) • Myelodysplastic/Myeloproliferative disease (OI)
Interferon beta-1a (Avonex), IM	• None	• Multiple sclerosis (OI)
Lenalidomide (Revlimid), PO	• Treatment of multiple myeloma (MM) as (1) maintenance following autologous hematopoietic stem cell transplantation (auto-HSCT) and (2) in combination with dexamethasone for the treatment of patients with multiple myeloma who have not received at least one prior therapy (firs line treatment) • Treatment of mantle cell lymphoma whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.	• Multiple myeloma (second line) (OI) • Myelodysplastic syndromes (OI) • Other off-label supported uses

Table 4. Top 10 selling US drugs with orphan indications in 2016 [3,7,31]

Generic name (Brand name), route	Rare disease for which an orphan approval remains protected by the 7 year marketing exclusivity term[7]	Other rare diseases for which the approval exclusion period has expired and other non-orphan indications
Nivolumab (Opdivo), IV	• Melanoma with involvement of lymph nodes or metestatic disease who have undergone complete resection • Hepatocellular carcinoma • Classical Hodgkin lymphoma (relapsed or progressed) • Unresectable or metastatic melanolma (BRAF V600 wild-type)	• Colorectal cancer, metastatic (microsatellite instability-high or mismatch repair deficient) • Head and neck carcinoma, squamous cell (recurrent or metastatic) • Non-small cell lung cancer, metastatic, progressive • Renal cell carcinoma, advanced • Urothelial carcinoma, locally advanced or metastatic
Rituximab (Rituxan), IV	• Wegener's Granulomatosis, Microscopic Polyangiitis, and Churg-Strauss Syndrome • Chronic lymphocytic leukemia • Diffuse large B-cell lymphoma • Follicular lymphoma	• Non-Hodgkin B lymphoma (OI) • Rheumatoid arthritis • Other off-label supported uses
Sodium oxybenzatate (Xyrem), PO	• None	• Cataplexy in narcolepsy (OI) • Excessive day time sleepiness in narcolepsy

Abbreviations: IM, intramuscularly; IV, intravenously; OI, orphan indication approved for this disease state; PO, orally; SQ, subcutaneously

- Of the 5 injectable medications in Table 4, only 2 (Velcade [bortezomib] and Copaxone [glatiramer acetate]) are available as generics.
- Medicaid prior-authorization (PA) criteria and/or PDL placement includes the following: Avonex and Copaxone 20 mg are preferred agents on the current Utah PDL. Xyrem has PA-criteria set in place.[29,30]

ii. Forecasted top selling injectable orphan drugs for 2022 (worldwide) include the following: Opdivo, Keytruda, Darzalex, Soliris, Yervoy, Rituxan.[3] Orphan drugs are anticipated to account for 21% of worldwide brand-name prescription drug sales by 2022.[3]
   - Utah Medicaid PA-criteria currently exists only for Soliris.[29]

III. Spinraza (nusinersen) for Spinal Muscular Atrophy

Nusinersen is the first and only disease modifying agent approved for all phenotypes of spinal muscular atrophy (SMA), a neurodegenerative disease related to mutations among the survival motor neuron 1 gene (SMN1).[32,33] Currently, no other disease-modifying treatment options exist for SMA; only supportive/symptomatic treatments are available. For the majority of cases, however, nusinersen treatment does not restore normal motor function, as it is not a cure for SMA. Most SMA patients will continue to require orthopedic, nutritional, or pulmonary supportive care while on nusinersen treatment.

Spinal Muscular Atrophy (SMA) Overview

Spinal muscular atrophy results from mutations, deletion or point mutations, in the SMN1 gene, which impair the production of spinal motor neuron protein (SMNp).[32,34] The majority of cases are due to an autosomal recessive inheritance; however, there have been a few case reports of carriers (with only 1 functional copy of the SMN1 gene) becoming symptomatic later in life.[35] Deficiency of SMNp results in loss of alpha-motor neurons in the brainstem and spinal cord; muscle weakness of the limbs, trunk, and respiratory muscles; and profound physical disability.[32,36,37] The incidence of SMA is estimated between 1 in 6000 to 11,000 live births and "is the most common genetic cause of infant death," with most deaths occurring before age 2.[32,38] The age of onset is a predictor of the person's maximal motor function, with earlier onset associated with more severe disease.[37] Onset occurs before 6 months of age in about 60%[36] of affected individuals; these patients usually do not live past 2 years old.

Respiratory complications are the major cause of morbidity and mortality in SMA, which include impaired clearance of lower airway secretions, hypoventilation, and recurrent infections.[33] Other physiological disturbances include feeding and swallowing difficulties, gastrointestinal dysfunction, cardiac structural and autonomic dysfunction, irregular bone remodeling, and immune dysfunction.[37,39] Pain is a common complaint that may result from constipation, infections, fractures, gastrointestinal reflux, pressure sores, scoliosis/hip subluxation, muscle cramping/spams, surgical intervention, etc.[40] Nutritional, respiratory, and orthopedic therapy and/or surgery are commonly required, especially for infant/child-onset SMA.[33,37] Patient and caregiver quality of life is greatly affected as physical independence is lost.

Humans have two genes encoding SMNp: survival motor neuron 1 gene (SMN1) and survival motor neuron 2 gene (SMN2).[34] In healthy individuals, SMN1 produces the majority of SMNp, while SMN2 produces only low levels (5-10% of the normal amount).[34] Although SMNp production via SMN2 is insufficient to completely compensate for mutated SMN1 during SMA disease, its contribution helps nonetheless. The severity of SMA is inversely associated with the number of SMN2 copies that a person carries, which varies from person to person.[37,41] There are a range of SMA phenotypes. Table 5 displays the type classifications for SMA, representing the age of onset and usual maximal motor ability. There is variability within types so additional subtype classifications have also been proposed—representing a phenotypic continuum.[37,38,42]

Table 5. Classification of spinal muscular atrophy[32,33,37]

	Onset	Maximal Motor Milestone[37]	Prognosis	Select Presentation Features [43-46]	Other information
Type 0	Prenatal	None	Death before or shortly after birth	• Severe hypotonia	Patients experience rapid motor function decline[42]
Type 1	Before 6 months of age	None; usually can't roll, sit, or stand independently[47]	Death most likely before age 2[32]	• Severe muscle weakness/atrophy • Bell shaped chest • Bulbar dysfunction • Difficulty swallowing/cough • Usually require ventilator support • Underweight	"… the median age to death or ventilation (>16 hours per day) is 13.5 months and 10.5 months for patients with 2 copies of SMN2."[37]
Type 2	7 to 18 months	Sitting; can't stand independently	~93% survive to 25 years old[37]	• Weak swallowing/cough • May develop scoliosis • Joint contractures • Frequent pneumonias • Nocturnal hypoventilation • Oxygen desaturations	
Type 3	Childhood or adolescent years	Walking	Normal expected lifespan	• Obstructive apnea • Proximal muscle strength becomes weaker as patient ages • May experience frequent falls and fatigue • +/- bulbar dysfunction • At risk for scoliosis, lordosis, and joint contractures	Some lose the ability to walk[32]
Type 4	Adulthood	Normal	Normal expected lifespan	• Mild motor impairment	Likely to have a delay in diagnosis as presentation is confused with other diseases (this may also happen in other SMA types)

Diagnosis

Genetic testing is the standard diagnostic test for SMA, which is supported in the 2007 Consensus Statement for Standard of Care in Spinal Muscular Atrophy. Since the majority of patients (95-98%)[48] have deletions in SMN1, the authors describe that the SMN gene deletion test should be the first diagnostic test ordered when SMA is suspected.[33] This test has a 95% sensitivity and close to 100% specificity. It typically takes between 2 and 4 weeks to return depending on the laboratory used. The consensus statement states, "A homozygous deletion of SMN1 exon 7 (with or without deletion of exon 8) confirms the diagnosis of SMN-associated spinal muscular atrophy (5q spinal

muscular atrophy)."[33] There are also other situations that may lead to SMN1-related SMA such as when a patient has only one copy SMN1 with subtle mutations, "…rendering homozygous dysfunction of the gene."[33] The 2007 Consensus Statement for Standard of Care in Spinal Muscular Atrophy provides a diagnosis algorithm and describes testing for other non-SMN1-related spinal muscle atrophy diseases that may present with overlapping symptomatology.[33]

Assessment tools for motor development

- The Hammersmith Infant Neurological Exam Section 2 (HINE-2) includes: 8 main motor-milestone categories (voluntary grasp, kicking, head control, rolling, sitting, crawling, standing, and walking) with each having subcategories to track incremental changes in functional gain that leads up to achieving the milestone. The maximum total score possible is 26. By 18 months, more than 90% of healthy toddlers are able to achieve each milestone.[49] This scale been used for SMA type 1 patients.[47,50,51]
- The Hammersmith Functional Motor Scale Expanded (HFMSE) is designed for ambulatory SMA patients. The assessment includes 33 items total, with 66 maximal points). Per-item scores range from 0 to 2, with higher scores representing a higher degree of motor ability.[52] This assessment was employed in the phase 3 CHERISH nusinersen study for late-onset SMA.[53] Furthermore, authors of the CHERISH study note, "A change in the HFMSE score of at least 3 points is considered to be clinically meaningful."[54,55]
- The CHOP-INTEND[56] includes 16 items, each of which is scored based on a 0 to 4 point scale (0 for no response, 1 for minimal, 2 for partial, 3 for nearly full, 4 for complete). The maximum total score possible is 64. It has been validated for use in SMA type 1 infants.[42]
- The Compound muscle action potential (CMAP) amplitude was used in the ENDEAR study.

Spinraza (nusinersen)

Nusinersen is an antisense oligonucleotide that amplifies the amount of full-length SMNp produced via the SMN2 gene. It does this by inhibiting splicing at the downstream intron of exon 7 on the SMN2 transcript that would otherwise produce a truncated, less-stable SMN protein. This is a large molecule drug (7501 daltons) that must be intrathecally injected directly into the spinal cord.

Patients require 6 doses of nusinersen in the first year of treatment, then 3 doses yearly (administered 4 months apart) thereafter.[57] Nusinersen is metabolized by exonucleases and is not influenced by CYP450 enzymes. It's terminal half-life is 135 to 177 days in the cerebral spinal fluid and it is primarily excreted through the urine.[57] Table 6 provides a summary of the dosing and use concerns for nusinersen.

Serious adverse event risks include rare but potentially life-threatening thrombocytopenia and renal toxicity, which have been observed in clinical trials and are known class-effects of oligonucleotides with a phosphorothioate backbone.[53] To minimize these risks, the FDA placed product label warnings and recommendations to monitor the following laboratory parameters at baseline, prior to each dose, and as clinically needed: platelet count, prothrombin time, activated partial thromboplastin time, and quantitative spot urine.[57]

Post-marketing adverse-event case reports include serious infections, such as meningitis, and hydrocephalus. Upon the approval of nusinersen, the FDA required a postmarketing study pertaining to the development of anti-drug antibodies to identify potential negative effects or potential loss of effectiveness. The sponsor is to submit this report to the FDA in June of 2018.[58]

Lumbar Puncture Treatment Setting— Hache et al., provide guidance for administering nusinersen via lumbar puncture. Authors explain that lumbar puncture is generally a safe, however, "…side effects such as headache, back pain, and transient or persistent cerebrospinal fluid leakage (post–lumbar puncture syndrome), have been documented."[59] The procedure may be technically challenging if a patient with SMA also has scoliosis.[59]

The FDA's risk assessment review cites Hache et al, as the author describes that prescribers of nusinersen are expected to be pediatric neurologists or other members of the multidisciplinary clinical team.[59,60] Administration is expected to be carried out by neurologists, radiologists, and pediatric anesthesiologists in a variety of hospital settings. Practitioners may need to employ imaging or sedation during the procedure; thus, administration may be carried out in the following settings: interventional radiology departments, affiliated outpatient clinics, and the operating room.[59,60]

Table 6. Spinraza indications, dosing, and use concerns[17]

Dosage Form & Storage	**Spinraza- nusinersen**, 12 mg/5 mL solution (single dose vial) for intrathecal administration; before opening, store under refrigeration at 36-46°F; must be protected from light. Total combined time out of refrigeration (when removing and returning to storage) should not exceed 30 hours (at no more than 77°F), with the exception of the following: • Can be stored up to 14 days at or below 86°F prior to administration
FDA Approved Indications	**Spinal muscular atrophy (SMA) in pediatric and adult patients** (approved December 2016):
Dosage & Administration	**Dosing** **Loading dose**: initiate with 4 loading doses (12mg each – administered intrathecally)—the first three doses should be administered at 14-day intervals, followed by the 4th loading dose 30 days later **Maintenance dose**: a maintenance dose (12mg intrathecally), should be administered once every 4 months following the last loading dose. **Administration:** Intrathecal only • Should be administered by or under the direction of healthcare professionals experienced in performing lumbar punctures using aseptic technique • Must administer within 4 hours of removing drug from the vial into syringe • Consider sedation and ultrasound or other imaging techniques to guide intrathecal administration • Prior to administration, remove 5 mL of cerebrospinal fluid • Administer as an intrathecal bolus injection over 1 to 3 minutes using a spinal anesthesia needle • Do not administer via areas of the skin where there are signs of infection or inflammation
Warnings, Precautions & Adverse Reactions	**Contraindications**: None **Thrombocytopenia and coagulation abnormalities**: In the clinical study, 11% of treated patient developed a transient low platelet count, however no patients experienced a levels below 50,000 cells/microliter. Coagulation abnormalities and thrombocytopenia have been observed after administration of some antisense oligonucleotides. **Renal toxicity:** higher rates of urine protein elevation occurred in treated patients (33%) vs. controls (20%) in clinical trials. In general, renal toxicity has been observed after administration of some antisense oligonucleotides. **Common adverse reactions:** • In the infant population (occurring at least 5% more frequently than in control patients) lower respiratory infection, upper respiratory infection, and constipation; a serious adverse reaction was atelectasis • In the late onset population: headache, back pain, and post lumbar puncture syndrome **Other serious reactions/side effects:** the package insert discusses case reports of: • Severe hyponatremia • Rash (skin ulcers, and spontaneous resolution with continued Spinraza treatment) • Possible reduction in growth (as measured by height) • Serious infections including meningitis and hydrocephalus • Post marketing experience: case reports of serious infections, including meningitis, and hydrocephalus have occurred in patients treated with nusinersen
Monitoring	The following tests should be assessed at baseline, prior to each dose, and as clinically needed • Platelet count • Prothrombin time; activated partial thromboplastin time • Quantitative spot urine protein testing

Clinical Trial Information

Nusinersen was approved in December 2016 for all SMA types. Studies with different levels of evidence were provided to the FDA for the various SMA types. Randomized controlled trial (RCT) evidence was provided for children with SMA up to 12 years old at treatment initiation (most closely representing SMA Type 1 and Type 2 subpopulations). Non-controlled, open-label data was provided for other SMA types (adult-onset and pre-symptomatic SMA).[61] The fast-track review process for nusinersen was executed with close involvement and study design advice from the Division of Neurology Products among the FDA.[62] This led to a seamless and prompt approval granted nearly one month after the complete application was filed.[62]

An interim analysis of the ENDEAR Phase 3 trial (after 183 days of treatment or 4 doses of nusinersen) provided pivotal efficacy data for infant-onset SMA patients. There was a significant difference in the proportion of motor milestone responders favoring the treatment group: 41% (21/51) in the nusinersen group versus 0% (0/27) in the sham-control group, ($p<0.001$). Nonetheless, it is difficult to interpret the effect magnitude or the degree to which functional status improved since this RCT used a "…dichotomized [primary] endpoint that does not capture the mean treatment effect."[19] The FDA Office Director Memo describes the degree of meaningful benefit resulting from 6 months of nusinersen treatment as follows:

> "Although the response was clearly important, perhaps life-changing in a few cases (6% of patients gained the ability to sit without assistance, a feat that almost never occurs in individuals with only 2 copies of the SMN2 gene), the majority of patients had a modest response or no response at all."[61]
>
> "Thus, most (94%) of patients were not able to sit, no patient was able to stand unassisted, and no patient achieved walking. Compared to motor development in normal individuals, the response to nusinersen would have to be considered disappointing."[61]

In the published final analysis, significantly more infants in the nusinersen group had a motor-milestone response compared to the control group (37 of 73 infants [51%] vs. 0 of 37 [0%]). Comparing the nusinersen group to the control group, 22% of infants achieved full head control vs. 0%; 10% were able to roll over vs. 0 %; 8% were able to sit independently vs. 0%; and 1% were able to stand vs 0%. Overall risk of death or the use of permanent assisted ventilation was 47% lower in the treatment group compared to control (hazard ratio 0.53; $P = 0.005$).[50]

The primary endpoint definition from the trial was the *proportion of patients with a motor-milestone response*. Motor-milestone response was defined as meeting the following two criteria: (1) improvement in at least one of the following 7 HINE-2 categories (i.e., an increase in the score for head control, rolling, sitting, crawling, standing, or walking of ≥1 point, an increase in the score for kicking of ≥2 points, or achievement of the maximal score for kicking) and (2) more categories with improvement than categories with worsening. The total HINE-2 score range was 0 to 23. Assessments were scheduled for screening, and before lumbar puncture procedure on days 183, 302, and 394. Further information about the ENDEAR trial is provided in Table 7.

Following approval of nusinersen, the phase 3 trial in later-onset SMA pediatric patients was just recently published in February 2018. The CHERISH study enrolled patients between 2 to 12 years old, with symptom onset occurring after 6 months old (most patients having a diagnosis of Type 2 SMA).[61] The primary endpoint was the least-squares mean change from baseline in the total HFMSE score at month 15. At the interim analysis, there was a significant improvement favoring the treatment group (least squares mean difference in change, 5.9 points; 95% CI, 3.7 to 8.1; P<0.001). Similarly, in the final analysis, a significantly more positive difference from baseline in the HFMSE score was in favor of nusinersen (least-squares mean difference in HFMSE change, 4.9 points; 95% CI, 3.1 to 6.7).[54] Regarding secondary endpoints, although there were significantly more patients in the treatment group with an increase in the HFMSE score of at least 3 points (57% vs. 26%, P<0.001), there was no significant difference in the number of patients who achieved at least one World Health Organization motor milestone compared to the controlled group.[54] Further information about the CHERISH trial is provided in Table 7.

Table 7. Published phase 3 trial information[50,54]

Brief Trial Overview	**ENDEAR**: 13 month, international, DB-RCT assessing NUS versus a sham procedure in infants with SMA. Patients had documentation of a homozygous deletion or mutation in SMN1, two copies of SMN2, and with onset of SMA before 6 months of age. A total of 122 patients were randomized into the treatment groups. The two primary endpoints included (1) the proportion of patients with a motor-milestone response, according to the Hammersmith Infant Neurological Examination Section 2 (HINE-2) assessment and (2) the event-free survival defined as the time to death or the use of permanent assisted ventilation and stratified based on disease duration of more or less than 12 weeks (age at screening minus the age of symptom onset).	**CHERISH:** a 15 month, international, DB-RCT assessing NUS versus a sham procedure in pediatric patients (2-12 years old at screening) with SMA. Patients had genetic documentation of 5qSMA, 2-4 copies of SMN2, onset of SMA after 6 months of age, and the ability to sit independently. A total of 126 patients were randomized into the treatment groups and stratified by age (greater or less than 6 years old).
Key Eligibility Criteria	Children with infantile-onset SMA: • genetic diagnosis of 5q-linked spinal muscular atrophy (SMA) due to homozygous gene deletion or compound heterozygote deletion/mutation of SMN1 • 2 copies of SMN2 • younger than 6 months of age at SMA symptom onset and younger than 7 months of age (210 days) at screening • receiving adequate nutrition and hydration (with or without gastrostomy) in the opinion of the site investigator; measuring to at least the third percentile in body weight using country-specific guidelines • adherence to the consensus statement for standard of care in SMA • gestational age of 37 to 42 weeks • ability to complete all study procedures and parent/guardian has adequate psychosocial support	Children with later-onset SMA: • genetic diagnosis of 5q-linked spinal muscular atrophy (SMA) due to homozygous gene deletion or compound heterozygote deletion/mutation of SMN1 • onset at greater than 6 months of age • males/females between 2 and 12 years old at screening • able to sit independently, but never had ability to walk independently (ability to walk defined as ≥15 ft) • have a HFME score ≥ 10 and ≤ 54 at screening • have an estimated life expectancy of > 2 years from screening • meet age-appropriate institutional criteria anesthesia and sedation, if use is planned for study procedures

Exclusion Criteria	• peripheral oxygen desaturation (O2 saturation below 96% without ventilation support) during screening) • SMA symptoms within the first week of birth • presence of an active infection requiring systemic antiviral or antibacterial treatment during screening • history of brain or spinal cord disease that would interfere with lumbar punctures, cerebrospinal fluid circulation, or safety assessments; presence of an implanted cerebrospinal fluid drainage shunt or central nervous system catheter; • abnormalities in hematology or clinical chemistry parameters at screening that would prevent inclusion as assessed by the site investigator; • treatment of SMA with an investigational drug, biological agent, or device within 30 days of screening; history of gene therapy, prior antisense oligonucleotide therapy, or cell transplantation; the parent/guardian is unable to understand a basic description of the study or does not agree to comply with the schedule of assessments as defined by the protocol; the infant's caregiver does not adhere to the standard-of-care guidelines; presence of a medical condition that would interfere with the infant's ability to participate in the study as assessed by the site investigator	• Respiratory insufficiency, defined by the medical necessity for invasive or non-invasive ventilation for greater than 6 hours during a 24 hour period, at screening • Gastric feeding tube use, where the majority of feeds are given by this route • Severe contractures or severe scoliosis evident on X-ray • Hospitalization for surgery within 2 months of screening or planned during the duration of the study • Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the screening period. History of bacterial meningitis • History of brain or spinal cord disease or abnormalities by MRI or CT that would interfere with the LP procedures or CSF circulation • Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter • Prior injury or surgical procedure which impacts the subject's ability to perform any of the outcome measure testing required in the protocol and from which the subject has not fully recovered or achieved a stable baseline • Clinically significant abnormalities in hematology or clinical chemistry parameters or ECG • Treatment with another investigational drug, valproate, or hydroxyurea within 3-months of screening. Any history of gene therapy, antisense oligonucleotide therapy, or cell transplantation. • Ongoing condition that would interfere with the conduct and assessments of the study (e.g., wasting or cachexia, severe anemia, etc.) that would interfere with the assessment of safety or would compromise the ability of the subject to undergo study procedures
Interventions	**A. Intrathecal nusinersen procedure**: the dose was adjusted according to the estimated volume of cerebrospinal fluid for the infant's age to be equivalent to administering a 12-mg dose in a person 2 years of age or older **B. Sham procedure**: "The sham procedure consisted of a small needle prick to the skin over the lumbar spine, which was covered with a bandage to simulate the appearance of a lumbar-puncture injection." **Dosing on day 1, 15, 29 and 64, 183, and 302**	**A. Intrathecal nusinersen procedure**: 12mg per dose **B. Sham procedure**: "…consisted of a small needle prick to the skin over the lumbar spine, which was covered with a bandage to simulate the appearance of a lumbar-puncture injection." **Dosing on day 1, 29, 85 and 274**

Duration	A prespecified interim analysis occurred when enrollment achieved approximately 80 infants for at least 6 months. Upon finding a positive benefit–risk assessment in favor of nusinersen, the trial was terminated early. Assessments scheduled for day 394 were instead performed at the end-of-trial visit, 2 weeks after the patient received their last dose. Patients were invited to enroll in the open-label extension study SHINE (ClinicalTrials.gov number, NCT02594124).	A prespecified interim analysis was conducted when all patients had been enrolled for at least 6 months and at least 39 children had completed the 15-month assessment. A multiple-imputation method to account for missing data was used for those patients that did not have 15 month results at the interim analysis. Patients lacking a 15-month assessment were invited to attend a last visit (end of the double-blind visit) where all assessments scheduled for the 15-month assessment were captured. Patients were invited to enroll in the open-label extension study SHINE (ClinicalTrials.gov number, NCT02594124).
Endpoints	**Primary endpoints:** (1) proportion of patients with a motor-milestone response, according to the Hammersmith Infant Neurological Examination Section 2 (HINE-2) assessment (2) the event-free survival defined as the time to death or the use of permanent assisted ventilation. **Secondary endpoints:** (1) proportion of Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) responders (≥4-point score increase from baseline at the later of day 183, 302, or 394 assessments) (2) overall survival rate (3) percentage of infants not requiring permanent ventilation (4) proportion of compound muscle action potential (CMAP) responders (peroneal CMAP amplitude increasing to or maintained at ≥1 mV versus baseline at the later of day 183, 302, or 394 assessments) (5) two subgroup analyses of time to death or permanent ventilation in patients below the study median disease duration (6) two subgroup analyses for time to death or permanent ventilation in patients above the study median disease duration	**Primary end point:** (1) least-squares mean change from baseline in the total HFMSE score at month 15. (HFMSE assessments performed at 3, 6, 9, 12, and 15 months; authors cite that a change in the HFMSE score of at least 3 points is considered to be clinically significant. **Secondary end points** (1) percentage of patients who had an increase from baseline to month 15 in the HFMSE score of at least 3 points (2) percentage of patients who achieved at least one new World Health Organization motor milestone (out of a total of six milestones), (3) the change from baseline in the Revised Upper Limb Module (RULM) score (which ranges from 0 to 37, with higher scores indicating better function (4) proportion of children who had achieved the ability to stand alone or walk with assistance (5) change from baseline to month 15 in the HFMSE score according to age and disease duration

Final Analysis Results	• A significantly higher proportion of infants in the nusinersen group versus control group had a motor-milestone response (37 of 73 infants [51%] vs. 0 of 37 [0%]) • The likelihood of event-free survival was higher in the nusinersen group versus control group (HR for death or the use of permanent assisted ventilation, 0.53; P = 0.005). • The likelihood of overall survival was higher in the nusinersen group than in the control group (hazard ratio for death, 0.37; P = 0.004). Infants with a shorter disease duration at screening were more likely than those with a longer disease duration to benefit from nusinersen. The incidence and severity of adverse events were comparable between the treatment and control arm.	• A significantly larger proportion of children in the nusinersen arm compared to the control arm had an increase from baseline to month 15 in the HFMSE score of at least 3 points (57% versus 26%, P<0.001). • The overall incidence of adverse events was similar in the nusinersen group and the control group.

Abbreviations: DB-RCT, double blinded randomized control trial; HFMSE, Hammersmith Functional Motor Scale Expanded; HR, hazard ratio; NUS, nusinersen; SMA, spinal muscular atrophy

Utah Medicaid Utilization Data

- Utilization data for products previously referred to in Tables 2, 3, and 4 of this report is provided in Table 8. Data for agents abbreviated as IV (intravenous) and INJ (injectable) in Table 8 was obtained for the time period 2017 to January 12th, 2018. Data for agents abbreviated as SQ (subcutaneous) and IM (intramuscular) was obtained for the preparation of the previous DUR December 2017 orphan drug report covering the time period from October 2016 to October 2017.

Table 8. Utilization for injectable products listed in Tables 2, 3 and 4 (ACO+FFS)[a]

Route	Generic	Brand (s)	Rx claims (patient) counts	Indicated disease state(s)[c]
SQ	Adalimumab	Humira[b]	874 (177)	• Moderate to severe hidradenitis suppurativa (Hurley stage 2 and Hurley stage 3 disease) • Uveitis • Pediatric Crohn's disease • Treatment of juvenile rheumatoid arthritis • Rheumatoid arthritis • Ankylosing spondylitis • Crohn's disease • Juvenile idiopathic arthritis • Plaque psoriasis • Psoriatic arthritis • Ulcerative colitis
IV	Bevacizumab	Avastin[b]	874 (213)	• Cervical cancer, persistent/recurrent/metastatic • Colorectal cancer, metastatic • Glioblastoma, recurrent • Non-small cell lung cancer, nonsquamous • Ovarian (epithelial), fallopian tube, or primary peritoneal cancer • Renal cell carcinoma, metastatic
INJ	Bortezomib	Velcade[b]	141 (15)	• Mantle cell lymphoma first line • Multiple myeloma • Mantle cell lymphoma second line
IV	Brentuximab vedotin	Adcetris[b]	2 (1)	• Anaplastic large cell lymphoma • Hodgkin lymphoma • Mycosis fungoides
SQ	C-1 Esterase inhibitor	Haegarda[b]	10 (1)	For prevention of Hereditary Angioedema (HAE) attacks in adolescent and adult patients
SQ	Canakinumab	Ilaris[b]	11 (2)	• Cryopyrin associated periodic syndromes: familial cold autoinflammatory syndrome and Muckel-Wells Syndrome • Familial mediterranean fever • Hyper-IgD syndrome/Mevalonate Kinase Deficiency

Table 8. Utilization for injectable products listed in Tables 2, 3 and 4 (ACO+FFS)[a]

Route	Generic	Brand (s)	Rx claims (patient) counts	Indicated disease state(s)[c]
				• Systemic juvenile idiopathic arthritis • TNF receptor-associated periodic fever syndrome
IV	Daratumumab	Darzalex[b]	61 (3)	Multiple myeloma
SQ	Glatiramer Acetate	Copaxone (MEEA); Galtopa	189 (41)	Multiple sclerosis
IM	Interferon Beta-1a	Avonex[b]	89 (17)	Multiple sclerosis
IV	Ipilimumab	Yervoy[b]	2 (2)	Melanoma
IV	Pembrolizumab	Keytruda[b]	41 (16)	• Gastric cancer • Head and neck cancer, squamous cell • Hodgkin lymphoma • Melanoma • Microsatellite instability-high cancer • Solid tumors • Colorectal cancer • Non-small cell lung cancer • Urothelial carcinoma
IV	Nivolumab	Opdivo[b]	40 (9)	• Hepatocellular carcinoma • Classical Hodgkin lymphoma (relapsed or progressed) • Unresectable or metastatic melanolma (BRAF V600 wild-type) • Colorectal cancer, metastatic (microsatellite instability-high or mismatch repair deficient) • Head and neck carcinoma, squamous cell (recurrent or metastatic) • Non-small cell lung cancer, metastatic, progressive • Renal cell carcinoma, advanced • Urothelial carcinoma, locally advanced or metastatic
IV	Rituximab	Rituxan[b]	191 (50)	• Wegener's Granulomatosis, Microscopic Polyangiitis, and Churg-Strauss Syndrome • Chronic lymphocytic leukemia • Diffuse large B-cell lymphoma • Follicular lymphoma • Non-Hodgkin B lymphoma (OI) • Rheumatoid arthritis • Other off-label supported uses

Abbreviations: ACO, accountable care organization; FFS, fee-for-service; IM, intramuscular; INJ, injectable; IV, intravenous; MEEA, marketing exclusion has expired for all of the product's orphan-approved designations; OR, oral; Rx, prescription; SQ, subcutaneous

Table 8. Utilization for injectable products listed in Tables 2, 3 and 4 (ACO+FFS)[a]

Route	Generic	Brand (s)	Rx claims (patient) counts	Indicated disease state(s)[c]

[a] Data for IV and INJ agents was pulled for the time period (2017 to January 12th, 2018); Data for SQ and IM forms was pulled for the time period (October 2016 to October 2017); if a product is not listed, no utilization was found
[b] Notates a drug that only comes as a brand name product; where there is not an asterisk, the utilization data reflects that for the brand and generics
[c] See package inserts for the full FDA indication details

- Utilization data for the complete list of queried brand name injectable products (per Appendix B) is provided in Appendix C.

- Table 9 contains Medicaid utilization data for nusinersen among the fee-for-service population for 2017 to January 12th 2018.

Table 9. Spinraza (nusinersen) utilization data, fee-for-service population, 2017 to Jan. 12th, 2018

Claims (patient) counts	Query for ICD10 diagnosis codes: 335.1 , G12.0, G12.1, G12.8, G12.9 (see Appendix D for definitions)
<5 (<5)	All patient(s) had at least one of the above diagnosis codes

Discussion Topics for Developing Prescribing Criteria

❖ Potential Prior Authorization Criteria for Nusinersen

- **Based on indication**— PA criteria may require documentation of SMA confirmed by genetic testing and may include additional details (SMA type, number of SMN2 copies, age of onset, ventilator support status (hours/day), baseline renal function, motor function status)
    - Baseline motor function status may be required to help define the patient's response to therapy over time: may consider using the HINE-2 for SMA type 1 as used in the ENDEAR study or other assessments (e.g. HFMSE etc.) that may be appropriate for other SMA types
- Prescriptions may be limited to health care providers experienced in the treatment of neurological disorders (or in consultation with a pediatric neuromuscular specialist or neurologist specializing in SMA); administration should be conducted by providers with experienced in aseptic lumbar punctures
- Only the approved dose should be permitted
- **For continuation of therapy**, after e.g. 12 months, may consider requiring evidence of the following:
    - A lack of deterioration via documentation of maintained or improved motor function per motor milestone assessments at various time-points (e.g. prior to each dose) during treatment **OR**
    - maintenance of motor milestones to ages which they would be expected to be lost, or achievement of motor milestones unexpected considering their SMA type and SMN2 number (prescriber to provide rationale)
    - Note that patients may have an interruption in therapy for a planned surgery or during the management of a systemic infection, in which case, flexibility may be considered
- **Monitoring requirements** may be established per product labeling recommendations, recorded at baseline and prior to each dose: platelet count, prothrombin time; activated partial thromboplastin time, quantitative spot urine protein testing.
- A review of nusinersen PA-criteria may be considered after e.g. 12 months, after which the sponsor's study on anti-drug antibodies should be submitted to the FDA. If needed, additional criteria based on anti-body development may be constructed.

Summary

Rapid advancements in disease specific treatments, genetic characterization, and personalized medicine are driving the development of orphan drugs. Medications with orphan indications span a vast set of drug-classes and indications. Some FDA-approved orphan drugs have multiple orphan-designation approvals; some are additionally approved for common disorders.

Nusinersen is the first and only disease-modifying agent approved for patients with muscular atrophy (SMA), regardless of age and disease onset. Other than supportive/symptomatic treatments, no other treatment options are available. Nusinersen treatment is not curative. For most type 1 SMA patients, nusinersen is expected to provide modest or little improvement in motor function, while the risk of death or use of permanent assisted ventilation is significantly reduced. A few SMA type 1 patients may gain the ability to roll, sit, or stand from nusinersen treatment; however, most patients will continue to require supportive care such as orthopedic, nutritional, or pulmonary management. For later-onset pediatric patients, nusinersen is expected to increase the HFMSE score; published data from the most optimistic RCT suggests that at least half of treated patients may experience an increase of at least 3 points.

Topics encouraged for discussion include nusinersen PA-criteria based on the FDA indication, genetic diagnosis, trial criteria, demonstration of positive motor response, and recommended monitoring parameters.

Appendix A: Websites with Additional Background Information

CureSMA.org Educational Resources

Conference Medical Presentations

- http://www.curesma.org/support-care/for-healthcare-providers/educational-resources/

Orphanet.com

ICD10 coding recommendations for rare diseases

- http://www.orpha.net/consor/cgi-bin/Education.php?lng=EN

Prevalence and incidence of rare diseases

- http://www.orpha.net/consor/cgi-bin/Education.php?lng=EN

National Organization for Rare Disorders

Physician Guides for Rare Disorders

- https://rarediseases.org/for-patients-and-families/information-resources/physician-guides/

Appendix B: Orphan-Drug Master Table

Table 1: Injectable orphan drug subset (approvals from 1983 to December 2017)*

Generic Name	Trade Name (Route)
amphotericin B lipid complex	Abelcet (IV)
paclitaxel protein-bound particles	Abraxane (IV)
acetylcysteine	Acetadote* (IV)
tocilizumab	Actemra (IV)
corticorelin ovine triflutate	Acthrel (IV)
brentuximab vedotin	Adcetris (IV)
iobenguane I 123	Adreview (radiopharmaceutical)
laronidase	Aldurazyme (IV)
pemetrexed disodium	Alimta (IV)
copanlisib	Aliqopa (IV)
melphalan	Alkeran* (IV)
allopurinol sodium	Aloprim* (IV)
antihemophilic factor (human)	Alphanate (IV)
coagulation Factor IX (human)	Alphanine (IV)
coagulation factor IX (recombinant), Fc fusion protein	Alprolix (IV)
liposomal amphotericin B	Ambisome (IV)
benzoate/phenylacetate	Ammonul* (IV)
centruroides immune F(ab)2	Anascorp (IV)
antivenin crotaline (pit-viper) equine immune F(ab)2)	Anavip (IV)
obiltoxaximab	Anthim (IV)
anthrax immune globulin (human)	Anthrasil (IV)
fomepizole	Antizol* (IV)
nelarabine	Arranon (IV)
ofatumumab	Arzerra (IV)
ascorbid acid	Ascor (IV)
recombinant human antithrombin	Atryn (IV)
bevacizumab	Avastin (IV)
botulism immune globulin	Babybig (IV)
avelumab	Bavencio (IV)
belinostat	Beleodaq (IV)
bendamustine	Bendeka (IV)
coagulation Factor IX (recombinant)	Benefix (IV)
C1-esterase-inhibitor, human, pasteurized	Berinert (IV)
inotuzumab ozogamicin	Besponsa (IV)
blinatumomab	Blincyto (IV)
busulfan	Busulfex* (IV)

Table 1: Injectable orphan drug subset (approvals from 1983 to December 2017)*

Generic Name	Trade Name (Route)
caffeine	Cafcit* (IV)
alemtuzumab	Campath (IV)
protein C concentrate	Ceprotin (IV)
fosphenytoin	Cerebyx* (IV)
imiglucerase	Cerezyme (IV)
synthetic human secretin	Chirostim (IV)
C1 esterase inhibitor (human)	Cinryze (IV)
clofarabine	Clolar* (IV)
human factor X	Coagadex (IV)
factor XIII concentrate (human)	Corifact (IV)
isavuconazonium sulfate	Cresemba (IV)
antivenin, crotalidae polyvalent immune Fab (ovine)	Crofab (IV)
hydroxocobalamin	Cyanokit (IV)
ramucirumab	Cyramza (IV)
cytomegalovirus immune globulin (human)	Cytogam (IV)
decitabine	Dacogen* (IV)
daratumumab	Darzalex (IV)
desmopressin acetate	DDAVP* (IV, nasal, PO)
defibrotide	Defitelio (IV)
cytarabine lipisomal	Depocyt (Intrathecal)
diethylenetriaminepentaacetic acid (DTPA)	diethylenetriaminepentaacetric acid (IV)
digoxin immune FAB (Ovine)	Digibind (IV)
doxorubicin HCL liposome injection	Doxil* (IV)
clonidine	Duraclon* (Epidural infusion)
idursulfase	Elaprase (IV)
taliglucerase alfa	Elelyso (IV)
rasburicase	Elitek (IV)
epirubicin	Ellence* (IV)
buffered intrathecal electrolyte/dextrose injection	Elliotts B Solution (Intrathecal diluent for MTX, cytarabine)
antihemophilic factor (recombinant), Fc fusion protein	Eloctate (IV)
elotuzumab	Empliciti (IV)
epoetin alfa	Epogen (IV or SQ)
cetuximab	Erbitux (IV)
erwinia L-asparaginase	Erwinase (IV, IM, SQ)
ethanolamine oleate	Ethamolin (IV)
amifostine	Ethyol (IV)
melphalan	Evomela* (IV)
eteplirsen	Exondys 51 (IV)

Table 1: Injectable orphan drug subset (approvals from 1983 to December 2017)*

Generic Name	Trade Name (Route)
ceramide trihexosidase/alpha-galactosidase A	Fabrazyme (IV)
anti-inhibitor coagulant complex	Feiba (IV)
epoprostenol	Flolan* (IV)
pralatrexate	Folotyn (IV)
levoleucovorin	Fusilev* (IV)
immune globulin intraveous (human)	Gammaplex (IV)
immune Globulin (Human)	Gamunex(R)-C (IV)
obinutuzumab	Gazyva (IV)
polifeprosan 20 with carmustine	Gliadel (wafer for implant)
C1-esterase-inhibitor, human, pasteurized	Haegarda (IV)
eribulin mesylate	Halaven (IV)
hepatitis B immune globulin (human)	Hepagam (IV)
trastuzumab	Herceptin (IV)
antihemophilic factor/von Willebrand factor complex (human), dried, pasteurized	Humate-P (IV)
idarubicin	Idamycin* (IV)
recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP)	Idelvion (IV)
ifosfamide	Ifex* (IV)
talimogene laherparepvec	Imlygic (Intralesional injection)
morphine sulfate concentrate	Infumorph (Epidural/intrathecal)
interferon alfa-2b (recombinant)	Intron A (IM, SQ, or Intralesional)
romidepsin	Istodax (IV)
sebelipase alfa	Kanuma (IV)
prothrombin complex concentrate (human)	Kcentra (IV)
pembrolizumab	Keytruda (IV)
antihemophilic factor (recombinant)	Kogenate (IV)
pegloticase	Krystexxa (IV)
tisagenlecleucel	Kymriah (IV)
carfilzomib	Kyprolis (IV)
olaratumab	Lartruvo (IV)
sargramostim	Leukine (IV or SC)
baclofen	Lioresal* (Intrathecal)
ethiodized oil injection	Lipiodol (radiopaque contrast administered by anatomic area to be viewed)
gonadorelin acetate	Lutrepulse (IV or SQ)
voretigene neparvovec-rzyl	Luxturna (Intraocular injection)
technetium Tc 99m tilmanocept	Lymphoseek (injection)
vincristine sulfate LIPOSOME	Marqibo (IV)
trypan blue	Membraneblue (opthalmic injection)
vestronidase alfa-vjbk	Mepsevii (IV)

Table 1: Injectable orphan drug subset (approvals from 1983 to December 2017)*

Generic Name	Trade Name (Route)
mesna	Mesnex* (IV)
coagulation factor IX	Mononine (IV)
gemtuzumab ozogamicin	Mylotarg (IV)
N-acetylgalactosamine-4-sulfatase	Naglazyme (IV)
ibuprofen lysine	Neoprofen* (IV)
gallium [Ga-68]	Netspot (radiopharmaceutical, IV injection)
filgrastim	Neupogen (SQ or IV)
pentostatin for injection	Nipent (IV)
sodium nitrite and sodium thiosulfate	Nithiodote (IV)
biocarbonate infusate	Normocarb Hf (IV)
coagulation factor VIIa (recombinant)	Novoseven Rt (IV)
belatacept	Nulojix (IV)
antihemophilic factor (recombinant), porcine sequence	Obizur (IV)
pegaspargase	Oncaspar (IM or IV)
liposomal irinotecan	Onivyde (IV)
denileukin diftitox	Ontak (IV)
nivolumab	Opdivo (IV)
dexamethasone intravitreal implant	Ozurdex (Intravitreol implant)
hemin	Panhematin (IV)
pentamidine isethionate	Pentam 300 (IM or IV)
porfimer	Photofrin (IV)
idarucizumab	Praxbind (IV)
phoxilium	PrismaSol (IV)
alpha1-proteinase inhibitor (human)	Prolastin (IV)
aldesleukin	Proleukin (IV)
necitumumab	Protazza (IV)
methylene blue0.5%	Provayblue (IV)
edaravone	Radicava (IV)
raxibacumab	raxibacumab (IV)
antihemophilic factor (recombinant)	Refacto (IV)
infliximab	Remicade (IV)
treprostinil	Remodulin (SQ or IV)
fluocinolone	Retisert (Opthalmic implant)
zidovudine	Retrovir* (IV or PO)
human fibrinogen concentrate, pasteurized	Riastap (IV)
rifampin	Rifadin I.V. * (IV)
rituximab	Rituxan (IV)
coagulation factor IX (recombinant)	Rixubis (IV)
C1-esterase inhibitor (recombinant)	Ruconest (IV)

Table 1: Injectable orphan drug subset (approvals from 1983 to December 2017)*

Generic Name	Trade Name (Route)
dantrolene sodium suspension for injection	Ryanodex (IV)
synthetic porcine secretin	Secreflo (IV)
basiliximab	Simulect (IV)
eculizumab	Soliris (IV)
nusinersen	Spinraza (Intrathecal)
beractant	Survanta (Intrathecal)
siltuximab	Sylvant (IV)
paclitaxel	Taxol* (IV)
technetium Tc99m sulfur colloid injection, lyophilized	Technetium Tc99m Sulfur Colloi (radiopharm)
temozolomide	Temodar (PO and IV)
thiotepa	Tepadina (IV, intracavitary or intravesical)
antithrombin III (human)	Thrombate III (IV)
temsirolimus	Torisel (IV)
dexrazoxane	Totect* (IV)
bendamustine hydrochloride	Treanda (IV)
coagulation factor XIII A-subunit (recombinant)	Tretten (IV)
liothyronine sodium injection	Triostat* (IV)
arsenic trioxide	Trisenox (IV)
dinutuximab	Unituxin (IV)
valrubicin	Valstar (intravesical use)
bortezomib	Velcade (IV)
azacitidine	Vidaza* (IV)
elosulfase alfa	Vimizim (IV)
recombinant von Willebrand factor (rhVWF)	Vonvendi (IV)
glucarpidase	Voraxaze (IV)
velaglucerase-alfa	Vpriv (IV)
cytarabine, daunorubicin liposome injection	Vyxeos (IV)
Human plasma coagulation Factor VIII and human plasma von Willebrand Factor	Wilate (IV)
rho (D) immune globulin intravenous (human)	Winrho Sd (IM or IV)
collagenase clostridium histolyticum	Xiaflex (Intralesional)
antihemophilic factor (recombinant)	Xyntha (IV)
ipilimumab	Yervoy (IV)
axicabtagene ciloleucel	Yescarta (IV)
trabectedin	Yondelis (IV)
zoledronate	Zabel (IV)
ibritumomab tiuxetan	Zevalin (IV)
dexrazoxane	Zinecard* (IV)
zoledronate	Zometa* (IV)

Table 1: Injectable orphan drug subset (approvals from 1983 to December 2017)*

Generic Name	Trade Name (Route)

Abbreviations: IM, intramuscular; INJ, injectable; IV, intravenous; OR, oral; SQ, subcutaneous
*Products that appear to have AP generic equivalents per the FDA Orange Book
Note: Medicaid utilization for the intramuscular and subcutaneous injectable products is provided in the December 2017 DUR report, *"Overview of Drugs with Approved Orphan Indications: with Focus on Carbaglu*," so IM and SQ products are not re-queried for this report

Appendix C: Utilization for Injectable Branded Orphan Products

Table 1. Utilization for Branded Orphan Products (subset per Appendix B)—2017 to Jan. 12th, 2018, (FFS + ACO patients)[a]

Brand Name	Route									
	Epidural		Injection		Intrathecal		Intravenous		Intravitreal	
	Claims	Patients	Claims	Patients	Claims	Patients	Claims	Patients	Claims	Patients
ABRAXANE	-	-	-	-	-	-	**48**	**8**	-	-
ACETADOTE[b]	-	-	-	-	-	-	**<5**	**<5**	-	-
ACTEMRA	-	-	-	-	-	-	**95**	**11**	-	-
ADCETRIS	-	--	-	-	-	-	**<5**	**<5**	-	-
ALDURAZYME	-	-	-	-	-	-	**106**	**5**	-	-
ALIMTA	-	-	-	-	-	-	**25**	**9**	-	-
ALPHANATE	-	-	-	-	-	-	**25**	**<5**	-	-
ALPROLIX	-	-	-	-	-	-	**58**	**<5**	-	-
AMBISOME	-	-	-	-	-	-	**60**	**<5**	-	-
AVASTIN	-	-	-	-	-	-	**874**	**213**	-	-
BENDEKA	-	-	-	-	-	-	**77**	**7**	-	-
BENEFIX	-	-	-	-	-	-	**111**	**9**	-	-
CEREBYX[b]	-	-	**16**	**8**	-	-	-	-	-	-
CORIFACT	-	-	-	-	-	-	**9**	**<5**	-	-
DARZALEX	-	-	-	-	-	-	**61**	**<5**	-	-
DDAVP[b]	-	-	**6**	**<5**	-	-	-	-	-	-
DEPOCYT	-	-	-	-	**<5**	**<5**	-	-	-	-
DOXIL[b]	-	-	-	-	-	-	**<5**	**<5**	-	-
DURACLON	**7**	**<5**	-	-	-	-	-	-	-	-
ELAPRASE	-	-	-	-	-	-	**29**	**<5**	-	-
ELOCTATE	-	-	-	-	-	-	**12**	**<5**	-	-
EPOGEN	-	-	**4728**	**90**	-	-	-	-	-	-
ERBITUX	-	-	-	-	-	-	**6**	**<5**	-	-
EXONDYS 51	-	-	-	-	-	-	**<5**	**<5**	-	-
FABRAZYME	-	-	-	-	-	-	**<5**	**<5**	-	-
FEIBA	-	-	-	-	-	-	**10**	**<5**	-	-
GAMUNEX	-	-	20	**<5**	-	-	**15**	**<5**	-	-
GAZYVA	-	-	-	-	-	-	**<5**	**<5**	-	-
HALAVEN	-	--	-	-	-	-	**21**	**<5**	-	-
INFUMORPH	-	-	**<5**	**<5**	-	-	-	-	-	-
INTRON A	-	-	**<5**	**<5**	-	-	-	-	-	-
KEYTRUDA	-	-	-	-	-	-	**41**	**16**	-	-
KOGENATE	-	-	-	-	-	-	**60**	**9**	-	-
KRYSTEXXA	-	-	-	-	-	-	**16**	**<5**	-	-
LARTRUVO	-	-	-	-	-	-	**12**	**<5**	-	-
LIORESAL[b]	-	-	-	-	**5**	**<5**	-	-	-	-
NEUPOGEN	-	-	**372**	**59**	-	-	-	-	-	-
NOVOSEVEN RT	-	-	-	-	-	-	**23**	**<5**	-	-

NULOJIX	-	-	-	-	-	-	**<5**	**<5**	-	-
ONCASPAR	-	-	**26**	**10**	-	-	-	-	-	-
OPDIVO	-	-	-	-	-	-	**40**	**9**	-	-
OZURDEX	-	-	-	-	-	-	-	-	**30**	**16**
PANHEMATIN	-	-	-	-	-	-	**<5**	**<5**	-	-
PENTAM 300	-	-	**<5**	**<5**	-	-	-	-	-	-
PROLASTIN	-	-	-	-	-	-	**<5**	**<5**	-	-
PROVAYBLUE	-	-	-	-	-	-	**<5**	**<5**	-	-
REMICADE	-	-	-	-	-	-	**187**	**42**	-	-
REMODULIN	-	-	**36**	**5**	-	-	-	-	-	-
RETISERT	-	-	-	-	-	-	-	-	**<5**	**<5**
RITUXAN	-	-	-	-	-	-	**191**	**50**	-	-
SOLIRIS	-	-	-	-	-	-	**55**	**<5**	-	-
SPINRAZA	-	-	-	-	**<5**	**<5**	-	-	-	-
VELCADE	-	-	**141**	**15**	-	-	-	-	-	-
WILATE	-	-	-	-	-	-	**24**	**<5**	-	-
XIAFLEX	-	-	**<5**	**<5**	-	-	-	-	-	-
YERVOY	-	-	-	-	-	-	**<5**	**<5**	-	-
ZINECARD[b]	-	-	-	-	-	-	**<5**	**<5**	-	-
ZOMETA[b]	-	-	-	-	-	-	**<5**	**<5**	-	-

Abbreviations: ACO, accountable care organization; FFS, fee-for-service

[a] All other brand name products listed in Appendix B that are not listed here have zero utilization for the listed injectable types included for this table

[b] Denotes brand products that appear to have AP-generic equivalents listed in the FDA Orange Book

Appendix D: Relevant ICD10 Diagnosis Codes

ICD10 codes with “spinal muscular” term:

ICD	Diagnosis
3351	SPINAL MUSCULAR ATROPHY
G120	INFANTILE SPINAL MUSCULAR ATROPHY, TYPE I (WERDNIG
G121	OTHER INHERITED SPINAL MUSCULAR ATROPHY
G128	OTHER SPINAL MUSCULAR ATROPHIES AND RELATED SYNDRO
G129	SPINAL MUSCULAR ATROPHY, UNSPECIFIED

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