Abbreviated Drug Review

Trade Name (generic) Spinraza (Nusinersen)		
Estimated OHP Population: 1-5 patients Estimated Number of Live Births in OHP FFS: 27,100	Claims: 1-2 (estimated)	OHP Wholesale Acquisition Cost (WAC): Loading Dose Phase = $500,000 Maintenance Dose Phase = $375,000/year

Indications

- Spinal muscular atrophy in pediatrics and adults

Dosage

- Loading Dose - total of 4 doses as follows: 12 mg intrathecal once every 14 days for 3 doses; then 12 mg once 30 days after the third dose.[1]
- Maintenance Dose: 12 mg intrathecal once every 4 months.[1]

Administration of this drug should be directed by healthcare professionals experienced in performing lumbar punctures.

Background

Spinal muscular atrophy (SMA) is due to degeneration of motor neurons in the spinal cord, which causes progressive weakness, atrophy of skeletal muscles and hypotonia. SMA is one of the most frequent autosomal recessive diseases and the most common genetic cause of childhood mortality.[2] The phenotype is extremely variable, and patients are classified as SMA type 0-IV based on age at onset and clinical course. All types of SMA are caused by mutations in the survival motor neuron gene (SMN1). SMA Type I is the most common and severe type of SMA and occurs primarily in infants under 6 months of age.[3] These infants cannot sit unsupported and usually die within the first 2 years of life due to respiratory failure or infection. SMA type 4 generally occurs in the third decade of life and is the mildest form of the disease. The characteristics of each SMA type are described in **Table 1.**

Table 1. SMA classification and characteristics[3]

SMA Type	Age of Onset	Motor Function	Median Survival *	Incidence (per 100,000 live births)
0	Prenatal	Respiratory failure at birth	Weeks	N/A
I	0-6 months	Never able to sit unassisted	<2 years	3.2 – 7.1 (45% of cases)
II	6 - 18 months	Able to sit, but unable to independently walk	>2 years (~70% still alive at age 25)	1 – 5.3 (20% of cases)
III	18 - 36 months	Able to independently stand and walk, which may decline with disease progression	Normal	1.5 – 4.6 (30 % of cases)
IV	30 years	Ambulatory	Normal	N/A (5% of cases)

*Natural history may vary depending on supportive interventions

The standard diagnostic tool for SMA is genetic testing to assess for homozygous deletions or mutations in the SMN1 gene. Carrier testing is available and the incidence is estimated as 1:40 to 1:60.[3] There is no known cure for SMA. Management focuses on providing respiratory support, assisting with motor function as needed, and optimizing nutritional status. Pulmonary related complications are a major source of morbidity and mortality in severe cases of SMA. Difficulties in feeding and swallowing can lead to gastrointestinal complications and malnutrition.

Efficacy

Nusinersen is the first Food and Drug Association (FDA) approved therapy for treatment of SMA. This drug was fast tracked for FDA approval and phase III trial data for nusinersen has not yet been published. Nusinersen is an antisense oligonucleotide which increases exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) leading to production of full-length SMN protein. As a result, the amount of functional SMN protein increases and improves motor function in SMA patients who are deficient in SMN protein.

A phase 2, open-label, dose-escalation study assessed safety and efficacy in patients with infantile-onset SMA (EMBRACE).[4] Subjects enrolled in the trial were between 3 weeks and 7 months old with SNM1 homozygous gene deletion or mutation and SMA symptoms.[4] Clinical efficacy included event free survival and change from baseline of 2 motor function assessments: the Hammersmith Infant Neurological Exam Part 2 (HINE-2) and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) motor function test. HINE-2 measures seven different areas of infant development motor milestones as evaluated by a pediatric neurologist. Increase in score indicates improved function with a maximum score between 2 to 4 points for each category and a total maximum score of 26.[4] CHOP-INTEND is a validated 16 item scale (0-64 points) specifically designed to evaluate motor function by physical therapists in infants with SMA.[4] Twenty patients were included in the trial and followed from 2 to 32 months. The first 4 participants received a loading dose of 6 mg on days 1, 15 and 85 followed by 12 mg on day 253 and every 4 months thereafter. The next 16 subjects received 12 mg doses on the same schedule. There were 77 serious adverse events reported in 16 participants, all considered by study investigators not related or unlikely related to the study drug, with the most common being respiratory distress or failure or respiratory infections, which are commonplace in infants with spinal muscular atrophy.[4] Incremental improvements in developmental motor milestones on the HINE-2 were observed for 16 of 19 participants at the last visit compared with baseline.[4] Change in HINE-2 score from baseline to last visit was significant for both dosing cohorts

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combined (p=0.0002) and for participants in the 12 mg dose group (p<0.0001).[4] The data for HINE-2 score changes in the 6-12 mg cohort were not reported. Motor function, assessed using the CHOP-INTEND scale, showed a mean increase of 11.5 points from baseline to last visit overall (p=0.008; n=18), with 14 of 18 infants having an improvement.[4] In the 12 mg group, 12 of 14 participants had an increase from baseline to last visit (mean increase 15.2 points; p=0.0013).[4] The study did not mention the CHOP-INTEND score changes for the 6-12 mg group and did not mention individual scores before and after treatment. A second Phase II trial (NURTURE) focused on the efficacy of nusinersen in preventing or delaying the need for respiratory intervention or death in infants with genetically diagnosed and presymptomatic SMA is currently ongoing with anticipated results in 2019.

ENDEAR, is a phase 3, multicenter, randomized, double blind, multiple dose, placebo controlled study of nusinersen in 121 patients with infantile-onset SMA.[5] Participants were diagnosed with SMA symptoms before 6 months of age. The study is still ongoing and expected to reach completion July 2017.[5] The nusinersen dose used in the study is 12 mg intrathecally. The primary efficacy endpoint is responder analysis of motor milestones using the HINE-2 exam. A responder is defined as a patient who improved in more milestones than worsened. Survival analyses were completed on the intent-to-treat population. Eighty two patients were included in the interim efficacy population. A greater percentage of subjects achieved a HINE motor milestone response in the nusinersen group (40%; n=21 of 52) compared to the control group (0%; n=0 of 30) which was statistically significant (p <0.0001).[6] An analysis of overall survival found a lower percentage of subjects in the nusinersen group (15%) died compared with the control group (32%), although this was not statistically significant.[6] One additional Phase III trial (CHERISH) is currently ongoing in patients aged 2 to 12 years with later onset SMA with an estimated completion date of May 2017.[7]

Safety

The most common adverse reactions that were observed in patients were lower respiratory infection (43% with nusinersen vs 29% with placebo), upper respiratory infection (39% vs 34%) and constipation (30% vs 22%).[1] Coagulation abnormalities and thrombocytopenia have been observed after administration of nusinersen. Renal toxicity including potentially fatal glomerulonephritis has also been observed. Per the manufacturer, lab testing of platelets, prothrombin time and quantitative spot urine protein testing is recommended at baseline and prior to each dose of nusinersen.[1] For urinary protein concentrations > 0.2 g/L is it is recommended to consider repeat testing and further evaluation.[1]

Evidence Gaps/Limitations

Nusinersen is effective at improving motor function in infants with SMA. The long term impact on survival is not well documented due to the ongoing data collection in the phase III RCTs. Evidence regarding efficacy in adults is not published. Long term safety data is currently unavailable. As nusinersen is the first drug FDA approved to treat SMA, there are no comparator medications.

Recommendation

Implement prior authorization criteria to ensure nusinersen is used for funded conditions.

References

1. Prescribing Information Spinraza™ (nusinersen) Intrathecal Injection. Cambridge, MA. Biogen, Inc. December 2016. https://www.spinraza.com/en_us/home.html. Accessed February 15, 2017.
2. Wirth B. An Update of the Mutation Spectrum of the Survival Motor Neuron Gene (smn1) in Autosomal Recessive Spinal Muscular Atrophy (sma). *Hum Mutat*. 2000;15(3):228-237. doi:10.1002/(SICI)1098-1004(200003)15:3<228::AID-HUMU3>3.0.CO;2-9.
3. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. *Muscle Nerve*. 2015;51(2):157-167. doi:10.1002/mus.24497.
4. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet*. 2016;388(10063):3017-3026. doi:10.1016/S0140-6736(16)31408-8.
5. A Study to Assess the Efficacy and Safety of IONIS-SMN Rx in Infants With Spinal Muscular Atrophy - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/show/NCT02193074. Accessed February 15, 2017.
6. Spinraza Drug Information Submitted to the FDA for Approval. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209531Orig1s000RiskR.pdf. Accessed February 15, 2017.
7. A Study to Assess the Efficacy and Safety of IONIS-SMN Rx in Patients With Later-onset Spinal Muscular Atrophy - Tabular View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/record/NCT02292537. Accessed February 17, 2017.

Nusinersen

Goal(s):

- Approve nusinersen for funded OHP conditions supported by evidence of benefit (e.g. Spinal Muscular Atrophy)

Length of Authorization:

- Up to 12 months

Requires PA:

- Nusinersen

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Go to # 2	
2. Is this a request for continuation of therapy?	**Yes**: Deny: Refer request for renewal of therapy to DMAP medical director for review.	**No:** Go to #3
3. Does the patient have Spinal Muscular Atrophy (SMA) documented by genetic testing?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the drug being prescribed by a neurologist or a provider with experience treating spinal muscular atrophy?	**Yes:** Approve up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *3/17 (DM)*
Implementation *4/1/17*