DISCLAIMER

Our medical policies are designed for informational purposes only and are not an authorization, explanation of benefits or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

POLICY

INITIAL TREATMENT

Nusinersen may be considered medically necessary if conditions 1 to 6 are met:

1. Patient has a confirmed genetic diagnosis of spinal muscular atrophy (SMA) established by, or in consultation with a neuromuscular specialist/neurologist AND
2. Documentation of genetic test confirming 2 or more copies of SMN2 AND
3. Onset of SMA-associated signs and symptoms before 20 months of age. AND
4. Prescribed by a neurologist with expertise in treating SMA. AND
5. Initial approval is for 1 year limited to the Food and Drug Administration - approved dosing of 12 mg (5 mL) administered intrathecally per treatment with 4 loading doses; the first 3 loading doses should be administered at 14-day intervals. The 4th loading dose should be administered 30 days after the 3rd dose. A maintenance dose should be administered once every 4 months thereafter. AND
6. Patient is not concurrently enrolled in a clinical trial for any experimental therapy for SMA.

CONTINUATION OF TREATMENT

Incremental reauthorization for nusinersen for 1 year may be considered medically necessary if conditions 1 and 2 are met:

1. The patient was previously approved for nusinersen based on criteria 1 to 5 cited above AND
2. Documented evidence to support clinically meaningful improvement in motor milestones during previous treatment period.

Nusinersen is considered investigational for all other indications.
POLICY GUIDELINES

The recommended dose of nusinersen is 12 mg (5 mL) administered intrathecally. Treatment is initiated with 4 loading doses; the first 3 loading doses should be administered at 14-day intervals while the fourth loading dose is administered 30 days after the third loading dose. Maintenance doses should be administered once every 4 months thereafter.

BENEFIT APPLICATION

BLUECARD/NATIONAL ACCOUNT ISSUES

State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

BACKGROUND

SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is a rare autosomal recessive genetic disorder caused by homozygous deletions or variants in the SMN1 gene in chromosome 5. This gene is responsible for producing the “survival of motor neuron” protein (SMN1). As a consequence of absent or low levels of SMN1, the motoneurons in the spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk. During early development, these muscles are necessary for crawling, walking, sitting up, and head control. The more severe types of SMA can also affect muscles involved in feeding, swallowing, and breathing. The exact role of the SMN protein in motoneurons has not been completely elucidated, and levels of the SMN protein required for optimal functioning are unknown.\(^2\) SMN2 is a nearly identical modifying gene capable of producing nearly identical compensatory SMN2 protein. However, 70% to 90% of the transcripts produced from the SMN2 gene produce a truncated protein that is defective and unstable due to lack of exon 7.\(^2\) Further, humans exhibit variability (range, 0-6) in the number of copies of the SMN2 gene, and copy number is inversely proportional to severity of disease.\(^3\) These factors in tandem lead to wide variability in disease severity.

The prevalence of SMA is estimated to be between 9.1 and 10 per 100,000 live births.\(^4\)\(^5\)

Classification

SMA is classified into 4 main categories (with additional subcategories) based on the age at the onset of symptoms.\(^6\)\(^7\) Generally, early onset of disease directly correlates to the severity of symptom and rate of disease progression. There is no exact marker to classify these categories, and they are not well-distinguished by ICD-10-CM code.

- **Type 0**: The most severe form of SMA, symptoms can often be seen in the later stages of pregnancy. Fetal movements are less than expected and, after birth, the infant will have little ability to move and may not be able to breathe and swallow independently. Death occurs before the age of 6 months.

- **Type I** (also called infantile SMA or Werdnig-Hoffman disease and subcategorized as IA, IB, and IC): Onset within 6 months of birth and symptoms progress rapidly, with most infants dying before 1 year of age from respiratory failure. About 60% of patients with SMA constitute of this phenotype.\(^8\)\(^9\)
• Type II (also called intermediate SMA or Dubowitz disease): Onset is within 6 to 18 months with less severe progression. Typically, a child can sit independently if positioned, but is unable to walk. More than 70% of patients live beyond 25 years of age with adequate supportive care.

• Type III (also called Kugelberg-Welander disease and subcategorized as IIIA and IIIB): Onset is after 18 months of age. Lifespan is not affected, with wide-ranging reductions in muscle strength with a chronic course. The outcome depends primarily on the severity of muscle weakness at presentation rather than the age of onset, but earlier onset tends to correlate with greater weakness.10

• Type IV (also called adult-onset SMA): Onset usually presents in the third decade of life and is otherwise similar to type III SMA.

Diagnosis

In 95% cases, both copies of the SMN1 exon 7 are absent. The remaining 5% cases are compound heterozygotes for SMN1 exon 7 deletion and small intragenic variants. The molecular diagnosis of SMA consists of detecting the absence of exon 7 of the SMN1 gene in the majority of cases.11

Treatment

Nusinersen is a modified antisense oligonucleotide (a synthetic genetic material) that binds to a specific sequence in the intron downstream of exon 7 of the SMN2 transcript; nusinersen causes the inclusion of exon 7 in the SMN2 transcript, leading to the production of full-length functional SMN2 protein.12 Prior to approval of nusinersen, there were no treatments approved by the Food and Drug Administration for SMA. Medical management of SMA patients includes respiratory, digestive, and musculoskeletal supportive care.

REGULATORY STATUS

On December 23, 2016, nusinersen (Spinraza™; Biogen) was approved by the U.S. Food and Drug Administration for treatment of pediatric and adult patients with SMA.

RATIONALE

This evidence review was created in February 2017 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through February 5, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function - including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes.
and to assess generalizability to broader clinical populations and settings of clinical practice.

**TYPE I (INFANTILE-ONSET) SPINAL MUSCULAR ATROPHY**

The evidence base for infantile-onset or type I spinal muscular atrophy (SMA) is summarized in Table 1. This evidence base consists of 2 RCTs and 2 early-phase open-labeled studies. Results of a phase 2 RCT trial (EMBRACE) are not available and not discussed further.

**Table 1. Summary of Key Trial Characteristics in Infantile-Onset or Type I SMA Patients**

<table>
<thead>
<tr>
<th>Study (Trial)</th>
<th>Trial Name</th>
<th>Design</th>
<th>Dates</th>
<th>Patients (N)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unpublisheda (NCT02462759)</td>
<td>EMBRACE</td>
<td>RCT</td>
<td>Aug 2015</td>
<td>Symptomatic (21)</td>
<td>Safety, tolerability</td>
</tr>
<tr>
<td>Unpublisheda (NCT02386553)</td>
<td>NURTURE</td>
<td>1 arm</td>
<td>May 2015</td>
<td>Presymptomatic (25)</td>
<td>Efficacy</td>
</tr>
</tbody>
</table>

PK: pharmacokinetics; RCT: randomized controlled trial; SMA: spinal muscular atrophy.

*aAvailable as abstract only.

**Symptomatic Patients**

The pivotal trial was a multicenter randomized, double-blind trial (ENDEAR; NCT02193074) in which 121 infants with a documented genetic diagnosis of SMA with symptom onset before 6 months of age were randomized 2:1 to nusinersen (n=80) or to sham injection (n=41). Patients were documented to have 5q SMA homozygous gene deletion, homozygous variant or compound heterozygote, and 2 copies of the SMN2 gene. With a sample size of 111, the trial had an 80% power to detect doubling of median time to death or permanent ventilation in the nusinersen group vs the sham-controlled group.13

Nusinersen was approved on the basis of planned interim analysis of 82 patients who completed at least 183 days of treatment or died or withdrew. Patients demographics at baseline were 44% male, and 87% white, with median length of treatment of 261 days (range, 6-442 days). The 2 treatment groups were balanced with respect to gestational age, birth weight, disease duration, and SMN2 copy number, except for age at symptom onset, use of ventilatory support, and the presence of symptoms specific to spinal muscular atrophy. These were higher in the nusinersen group than the control group. The primary end point was the proportion of motor milestone responders.

In the preplanned interim analysis, only the first primary end point was tested and a hierarchical testing strategy was used for the second primary end point and the secondary end points were used in the final analysis to control for overall type I error rate at 0.05. Results are summarized in Table 2.13 The trial met its coprimary end points, with nusinersen showing clinically meaningful improvement in motor milestones and probability of surviving or receiving permanent-assisted ventilation compared with sham control. The median time to death or the use of permanent-assisted ventilation was 22.6 weeks in the control group and was not reached in the nusinersen group. Multiple secondary end points (see Table 2) showed a consistency in treatment effect favoring nusinersen over sham control. Compared with control
group, infants in the nusinersen group reported a statistically significantly higher response percentage on the Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND; 71% vs 3%, p<0.001) and a lower percentage of deaths by the end of the trial (16% vs 39%; hazard ratio, 0.37; 95% confidence interval, 0.18 to 0.77; p=0.004). All subsequent secondary end point analyses were considered exploratory.

It is notable that half of nusinersen-treated subjects did not achieve the primary end point motor milestone response. The Food and Drug Administration (FDA; based on interim analysis) reported “although the response was clearly important, perhaps life changing in 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.” Further, FDA noted that 94% patients were not able to sit, no patient was able to stand unassisted, and no patient progressed to walking. On the motor response rate (using the Hammersmith Infant Neurologic Exam [HINE]), FDA concluded that, on average, mean motor milestone scores in nusinersen-treated patients improved from approximately 1 point (prior to treatment) to approximately 4 points at 12 months—a difference of 3 points over 6 months. At 12 months, a healthy baby would achieve a motor milestone score of 22. Thus, nusinersen is a disease-modifying treatment and not a cure. While no irreversible harms were observed in the preliminary clinical data analyzed by the FDA prior to drug approval, FDA noted that such harms cannot be ruled out based on animal toxicity data (potential of neurotoxicity) and class effects of antisense oligonucleotides (coagulation abnormalities, thrombocytopenia, renal toxicity). Given the limited data on durability of response, long-term data documenting safety and efficacy is needed.

Table 2. Summary of Results of Pivotal ENDEAR Trial

<table>
<thead>
<tr>
<th>Characteristics and Outcomes</th>
<th>Nusinersen</th>
<th>Sham-Controlled</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>80</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent motor milestone response (HINE section 2)a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interim analysisb</td>
<td>21/51 (40)</td>
<td>0/27 (0)</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Final analysisc</td>
<td>37/73 (51)</td>
<td>0/37 (0)</td>
<td>0.53 (0.32 to 0.89)</td>
<td>0.005</td>
</tr>
<tr>
<td>No death or use of permanent-assisted ventilationd</td>
<td>49/80 (61)</td>
<td>13/41 (32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4-point improvement in CHOP-INTEND score</td>
<td>52/73 (71)</td>
<td>1/37 (3)</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No death</td>
<td>67/80 (84)</td>
<td>25/41 (61)</td>
<td>0.37 (0.18 to 0.77)</td>
<td>0.004</td>
</tr>
<tr>
<td>No use of permanent-</td>
<td>62/80 (78)</td>
<td>28/41 (68)</td>
<td>0.66 (0.32 to 1.37)</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Nusinersen for Spinal Muscular Atrophy

<table>
<thead>
<tr>
<th>CMAP responsef</th>
<th>26/73 (36)</th>
<th>2/37 (5)</th>
<th>-</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>No death or use of permanent-assisted ventilation among those with disease duration ≤13.1 wk at screening</td>
<td>30/39 (77)</td>
<td>7/21 (33)</td>
<td>0.24 (0.10 to 0.58)</td>
<td>-</td>
</tr>
<tr>
<td>No death or use of permanent-assisted ventilation among those with disease duration &gt;13.1 wk at screening‡</td>
<td>19/41 (46)</td>
<td>6/20 (30)</td>
<td>0.84 (0.43 to 1.67)</td>
<td>-</td>
</tr>
</tbody>
</table>

Adapted from Finkel et al (2017).13 Values are percent or n (%) or as otherwise indicated.
CI: confidence interval; CMAP: compound muscle action potential; CHOP-INTEND: Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE: Hammersmith Infant Neurologic Exam; HR: hazard ratio.

aMotor milestone response was defined according to scores on the HINE-2, which assesses the development of motor function through the achievement of motor milestones; in this trial, the scores accounted for 7 of the 8 motor milestone categories, excluding voluntary grasp. Infants were considered to have a motor milestone response if they met the following 2 criteria: improvement in at least 1 category (ie, 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 more categories with improvement than categories with worsening (ie, a decrease in the score for head control, rolling, sitting, crawling, standing, or walking of ≥1 point or a decrease in the score for kicking of ≥2 points).
bPrespecified interim analysis conducted on June 15, 2016 included data from 78 infants who had at least 6 months of follow-up.
cFinal analysis conducted on November 21, 2016 included 121 data from infants who had undergone randomization and the assigned procedure at least once.
dPermanent-assisted ventilation was defined as tracheostomy or ventilatory support for at least 16 h/d for more than 21 continuous days in the absence of an acute reversible event, as determined by an independent end point adjudication committee.
eA CHOP INTEND response was defined as an increase of at least 4 points from baseline in CHOP INTEND score at the end-of-trial visit (day 183, 302, or 394).
fA CMAP response was defined as an increase in the peroneal CMAP amplitude to at least 1 mV (or maintenance of an amplitude of ≥1 mV) at the end-of-trial visit (day 183, 302, or 394).

Figure 1. Net Change From Baseline in Total Motor Milestone Score by Percentage of Patients in the Interim Efficacy Set
MP 5.01.28
Nusinersen for Spinal Muscular Atrophy

For subjects alive and ongoing in the trial, the change in total motor milestone score from the Hammersmith Infant Neurologic Exam was calculated the later of days 183, 302, or 394.

Supportive evidence also includes a published phase 2, open-labeled proof-of-concept study (NCT01839656) in which 20 patients with type I SMA with the onset of symptoms before 6 months of age were randomized to 2 doses of nusinersen (6 mg [n=4], 12 mg [n=16]). The study was completed in 2017 and results of the interim analysis done in January 2016 were published. Incremental improvements in motor milestones on the HINE-2 were observed in 84% (16/19) of patients at the last visit compared with baseline. Improvements of 2 points or more per motor milestone category for at least 1 category were observed in 68% (13/19) of patients. Mean increase in CHOP INTEND scores was 11.5 points from baseline to the last visit, with 78% (14/18) showing an improvement. Additional data from this study were suggestive of improvement in survival, permanent ventilation independence, and neuromuscular electrophysiology. Small sample size, short follow-up (2-32 months), and lack of a control group limit the interpretation of study results. Nevertheless, the data are indicative of potential benefit of nusinersen in type I SMA.

Section Summary: Type I (Infantile-Onset) Spinal Muscular Atrophy

The evidence for use of nusinersen for symptomatic type I (infantile-onset) SMA consists of 2 double-blind RCTs and a single-arm study. The largest phase 3 confirmatory ENDEAR trial (N=121) showed clinically meaningful and statistically significant improvement in motor milestones and event-free survival that exceeded those seen in the control group. However, most patients had a modest response or no response and only a small proportion of patients (6%) gained the ability to sit without assistance. On average, mean motor milestone score in nusinersen-treated patients improved by 3 points over 6 months. Given the limited data on durability of response, long-term data documenting safety and efficacy are needed.

Presymptomatic Patients

In a multicenter, single-arm, open-label trial (NURTURE; NCT02386553), 25 infants documented to have 5q SMA homozygous gene deletion, homozygous variant or compound heterozygote variant, and deemed likely to develop SMA type I or II (based on number of SMN2 copies) received nusinersen. Of
the 25 infants, 15 had 2 copies of SMN2 (most likely to develop Type 1 SMA) and 10 had 3 copies of SMN2 (most likely to develop Type II SMA). Age of infants at first dose ranged from 8 to 41 days (≤14 days, n=9; >14 to ≤28 days, n=12; >28 days, n=4). The trial is ongoing and interim results (median follow-up of 16.1 months) have presented as an abstract Muscular Dystrophy Association Clinical Conference on March 11-14, 2018, in Arlington, Virginia. The primary end point was time to death or respiratory intervention (invasive or noninvasive ventilation for ≥6 h/d continuously over for ≥7 days or tracheostomy). Multiple secondary end points related to motor improvement, growth, survival, need for ventilation, and electrophysiology were also assessed. At 365 days of the study visit, the mean CHOP INTEND total score (visual estimation from a graph) was 56 and 64 in patients with 2 and 3 copies of SMN2 respectively. The maximum score on CHOP INTEND is 64. Based on a natural history cohort of children with SMA with 2 SMN2 copies, the highest individual CHOP-INTEND score was 33 and mean score was 19.9 over a 2-year period.17 Among healthy children, the mean CHOP INTEND score was 56.7 at 3-months. At the time of data cut-off (July 5, 2017), all infants were alive and none required tracheostomy or permanent ventilation. Two of 15 (13%) infants with 2 SMN2 copies required respiratory intervention for ≥6 hours/day continuously for ≥7 days during an acute, reversible viral infection, and thus met the primary endpoint. All infants achieved the WHO motor milestone sitting without support, and 8/13 (62%; 2 SMN2 copies, n=3/8; 3 SMN2 copies, n=5/5) achieved walking alone. No new safety concerns were reported. While the FDA label has not been updated, it agreed with sponsor findings that the open-labeled uncontrolled trials such as NURTURE were consistent with the results of pivotal RCT and supported the efficacy of nusinersen in infantile SMA, including when given to presymptomatic patients. The prescribing label states: “some patients achieved milestones such as ability to sit unassisted, stand, or walk when they would otherwise be unexpected to do so, maintained milestones at ages when they would be expected to be lost, and survived to ages unexpected considering the number of SMN2 gene copies of patients enrolled in the studies.”12

Subsection Summary: Presymptomatic Type I (Infantile-Onset) Spinal Muscular Atrophy

The evidence for use of nusinersen for presymptomatic type I (infantile-onset) SMA consists of a single-arm study. It showed support for the efficacy as well as early initiation of nusinersen in infantile SMA patients because these patients achieved larger improvement in motor milestones compared indirectly with the natural history of SMA or healthy infants. Given the limited data on durability of response, long-term data documenting safety and efficacy are needed.

TYPE II OR III SMA

The evidence base for patients with type II or III SMA is summarized in Table 3.

Table 3. Summary of Key Trial Characteristics in Type II and III SMA Patients

<table>
<thead>
<tr>
<th>Study (Trial)</th>
<th>Trial Name</th>
<th>Design</th>
<th>Dates</th>
<th>N</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiriboga et al (2016) (NCT01494701)</td>
<td>CS1</td>
<td>1 arm</td>
<td>Nov 2011</td>
<td>28</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>Chiriboga et al (2016) (NCT01780246)</td>
<td>CS10</td>
<td>1 arm</td>
<td>Jan 2013</td>
<td>18</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>Unpublished (NCT01703988)</td>
<td>CS2</td>
<td>1 arm</td>
<td>Oct 2012</td>
<td>34</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>Unpublished (NCT02052791)</td>
<td>CS12</td>
<td>1 arm</td>
<td>Jan 2014</td>
<td>47</td>
<td>Safety and tolerability</td>
</tr>
</tbody>
</table>
RCT: randomized controlled trial; SMA: spinal muscular atrophy.

The evidence base for patients with type II and III SMA consists of 4 early-phase, open-labeled studies and a double-blind phase 3 RCT. Of these, results of 2 early-phase 1 studies and 1 double-blind phase 3 RCT20 have been published.19 However, data from phase 1 studies are not reviewed because they were early dose-finding and proof-of-concept studies. The remaining 2 studies - CS2 and CS12 - have not been published yet but data were sourced from the AMCP dossier supplied by Biogen (2016) and only summarized briefly at the end of this section.18

Similar to ENDEAR, CHERISH20 was also designed as a multicenter, randomized, double-blind trial that evaluated 126 nonambulatory patients with genetic documentation of 5q SMA (a homozygous deletion, variant, or compound heterozygote in SMN1) with the onset of signs and symptoms at more than 6 months and between ages 2 and 12 years at screening as well as the presence of the following features at screening: the ability to sit independently, no history of the ability to walk independently (defined as the ability to walk ≥15 feet unaided), and a Hammersmith Functional Motor Scale–Expanded (HFMSE) score between 10 and 54. Children were excluded if they had a severe contracture, evidence of severe scoliosis on radiography, respiratory insufficiency, or a gastric tube placed to provide adequate nutrition.

Because of the strict inclusion and exclusion criteria to enroll a homogenous and younger patient population (median age from 4 to 3 years in treatment and control group, respectively), the results from this trial have limited generalizability to type II and III SMA patients generally seen in clinical practice.

The primary end point was change in HFMSE score compared with baseline. HFMSE scores range from 0 to 66, with higher scores indicating better motor function. With a sample size of 117, the trial had 90% power to detect a mean difference of 3 points in HFMSE scores from baseline to 15 months between the trial arms at a 2-sided level of 0.05. Results are summarized in Table 4. The trial met its primary end points with nusinersen showing clinically meaningful improvement in mean HFSME scores compared with sham control. In terms of responder analysis, a higher percentage of children in the nusinersen group (57%) than in the control group (26%; p<0.001) had an increase from baseline to month 15 in the HFMSE score of at least 3 points, which was considered meaningful. Multiple secondary end points summarized in Table 4 showed a consistency in treatment effect favoring nusinersen compared with sham control. Approximately a quarter of placebo patients reported clinically meaningful improvements in HFMSE scores at 15 months, which is most likely a combination of placebo effect, the learning curve for the assessment of the HFMSE and Revised Upper Limb Module (RULM) scores, and initial developmental gains, particularly in younger children. Mean HFSME score plotted over time (data not shown) show that the initial improvement in HFSME scores in the placebo arm was short-lived and showed a declining trend starting at 6 months and continuing to the end of the trial (ie, 15 months). Analyses of magnitude of change in the HFMSE score stratified by age and disease duration (data not shown) revealed greater, improvements in younger children and in those who received treatment earlier in their disease course, respectively. The overall incidences of adverse events and moderate and serious adverse events were similar for the nusinersen group and the control group (93% and 100% vs 46% and 55%, respectively). Adverse events with an incidence of 5 or more percentage points higher in the nusinersen group than in the control group were pyrexia, headache, vomiting, back pain, and epistaxis. Given the limited data on durability of response, long-term data documenting safety and efficacy are needed.
Similar to ENDEAR trial, the confirmatory phase 3 CHERISH trial was terminated early because the results of a preplanned interim analysis met the primary end point of efficacy. However, in the prespecified interim analysis, data for the 15-month time-point for HFSME score were missing in 58% (49/84) and 55% (23/42) patients in the nusinersen and control group, respectively, and was imputed using the use of a multiple-imputation method to conduct an intention-to-treat analysis. The missing data were largely due to patients who had not completed their 15-month visit at the time of analysis. In the final analysis, the proportions of missing data for HFMSE and RULM scores were imputed for 21% (18/84) and 19% (8/42) patients in the nusinersen and control group, respectively, and imputed using multiple-imputation method to conduct an intention-to-treat analysis. For all other outcomes, only the observed data were included. The authors conducted multiple sensitivity analyses including (1) multiple imputations using mixed-effects model for repeated measures, (2) only completers (per protocol), (3) last-observation carried forward approach, and (4) for children who had a missing 15-month assessment and discontinued due to treatment failure or death, the worst of the last observed value or the baseline value was imputed. The intergroup difference between the least-squares mean change from baseline to month 15 remained statistically significant in favor of nusinersen in all 4 scenarios with highest treatment effect (change, 5.2) in the “completers only analysis”.

Table 4. Summary of Results of Pivotal CHERISH Trial

<table>
<thead>
<tr>
<th>Outcomes at 15 Months</th>
<th>Nusinersen</th>
<th>Control</th>
<th>Difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>84</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ in HFMSE score from baseline, LSM (95% CI)a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interim analysisb</td>
<td>4.0 (2.9 to 5.1)</td>
<td>-1.9 (-3.8 to 0)</td>
<td>5.9 (3.7 to 8.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Final analysisc</td>
<td>3.9 (3.0 to 4.9)</td>
<td>-1.0 (-2.5 to 0.5)</td>
<td>4.9 (3.1 to 6.7)</td>
<td>d</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with Δ in HFMSE score ≥3 points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent (95% CI)</td>
<td>57 (46 to 68)</td>
<td>26 (12 to 40)</td>
<td>30.5 (12.7 to 48.3)</td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>-</td>
<td>-</td>
<td>6 (2 to 15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients who achieved ≥1 new WHO motor milestone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Percent (95% CI)</td>
<td>20 (11 to 31)</td>
<td>6 (1 to 20)</td>
<td>14 (-7 to 34)</td>
<td>-</td>
</tr>
<tr>
<td>Δ from baseline in no. of WHO motor milestones achieved, LSM (95% CI)a</td>
<td>0.2 (0.1 to 0.3)</td>
<td>-0.2 (-0.4 to 0)</td>
<td>0.4 (0.2 to 0.7)</td>
<td>-</td>
</tr>
<tr>
<td>Δ from baseline in RULM score, LSM (95% CI)a</td>
<td>4.2 (3.4 to 5.0)</td>
<td>0.5 (-0.6 to 1.6)</td>
<td>3.7 (2.3 to 5.0)</td>
<td>-</td>
</tr>
</tbody>
</table>
MP 5.01.28
Nusinersen for Spinal Muscular Atrophy

Patients who achieved ability to stand alone

<table>
<thead>
<tr>
<th></th>
<th>Nusinersen</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Percent (95% CI)</td>
<td>2 (0 to 8)</td>
<td>3 (0 to 15)</td>
<td>-</td>
</tr>
</tbody>
</table>

Patients who achieved ability to walk with assistance

<table>
<thead>
<tr>
<th></th>
<th>Nusinersen</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Percent (95% CI)</td>
<td>2 (0 to 8)</td>
<td>0 (0 to 10)</td>
<td>2 (-19 to 22)</td>
</tr>
</tbody>
</table>

Adapted from Mercuri et al (2018).


a LSM change and LSM difference in change between groups were based on analysis of covariance with group assignment as a fixed effect and with adjustment for each child’s age at screening and the value at baseline.
b The interim analysis was conducted when all the children had been enrolled for at least 6 months and at least 39 children had completed the 15-month assessment. The proportions of missing data for 15 month time-point for HFSME score were 58% (49/84) and 55% (23/42) in the nusinersen and control group, respectively, and imputed using a multiple imputation method to conduct an intention-to-treat analysis.
c In the final analysis, the multiple imputation method was used for missing data to assess changes from baseline in the HFMSE score, percentage of children with a change in HFMSE score of at least 3 points, and change from baseline in the RULM score. The proportion of missing data for 15 month time-point for HFSME score were 21% (18/84) and 19% (8/42) in the nusinersen and control group, respectively, and imputed using a multiple imputation method to conduct an intention-to-treat analysis.
d Because the p value for the primary end point was significant in the interim analysis, this end point was not formally tested for significance in the final analysis.
e This value is an odds ratio rather than a difference. The odds ratio for nusinersen vs control was based on logistic regression, with group assignment as a fixed effect and with adjustment for each child’s age at screening and the HFMSE score at baseline.

CS2 is phase 1/2, single-arm study that was completed in January 2015. It included 34 patients between the ages of 2 and 15 with a documented genetic diagnosis of 5q SMA and clinical signs and symptoms attributed to SMA. Patients received various doses of nusinersen, ranging from 3 to 12 mg, with an average 8-month follow-up. The primary end point was safety, and the secondary end point was pharmacokinetic parameters. Multiple exploratory end points related to motor function were assessed including a change in HFMSE score. CS12 was a long-term extension study that included patients from CS2 and other studies. In the 6 patients with type II SMA, the mean change in HFMSE score after 1050 days of treatment was 12.3. In the 7 patients with type III SMA, the mean change in HFMSE score after 1050 days of treatment was 1.6.

Section Summary: Type II or III SMA

The evidence for use of nusinersen for patients with type II or III SMA consists of 4 single-arm studies and a double-blind RCT. The small single-arm studies employed multiple doses of nusinersen, ranging from 6 to 12 mg in patients with type II and III SMA. The available results did not stratify outcomes by dose or type of SMA and therefore it is difficult to interpret the data from these studies. The largest
phase 3 confirmatory CHERISH trial (126 patients) showed clinically meaningful and statistically significant improvement in motor milestones that exceeded those seen in the control group. Multiple secondary end points showed a consistency in treatment effect favoring nusinersen over sham control. Treatment effect was greater in younger children and in those who received treatment earlier in their disease course. Given the limited data on durability of response, long-term data documenting safety and efficacy are needed. Type 0 or IV SMA

There are currently no studies assessing efficacy and safety of nusinersen in patients with type 0 or IV SMA.

ADVERSE EVENTS

As per the prescribing label, thrombocytopenia (including acute, severe thrombocytopenia) and renal toxicity (including potentially fatal glomerulonephritis) have been observed with antisense oligonucleotides. In the controlled ENDEAR trial, the most common adverse events that occurred in at least 20% of nusinersen-treated patients and occurred at least 5% more frequently than in sham-controlled patients were lower respiratory infection, upper respiratory infection, and constipation. Atelectasis (a serious adverse event) was more frequent in nusinersen-treated patients (14%) than in sham-control (5%). Adverse events reported verbally were not assessable in the sham-controlled trial because patients were infants. In the open-labeled studies of patients with type II or III SMA, the most common adverse events were headache (50%), back pain (41%), and post-lumbar puncture syndrome (41%), which occurred within 5 days of lumbar puncture. Other adverse events in these patients were consistent with reactions observed in the controlled study. Also, 1 case of severe hyponatremia in an infant that required salt supplementation for 14 months and 2 cases of rash were reported. Both patients with rash continued to receive nusinersen and had a spontaneous rash resolution.

Development of anti-nusinersen antibodies was assessed in 126 patients of whom 5 (4%) developed treatment-emergent antidrug antibodies, of which 3 were transient, and 2 were persistent. There are insufficient data to evaluate an effect of antidrug antibodies on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.

SUMMARY OF EVIDENCE

Presymptomatic Patients With a Genetic Diagnosis Consistent With Type I or II SMA

For individuals who are presymptomatic with a genetic diagnosis consistent with spinal muscular atrophy type I or II presymptomatic individuals with a genetic diagnosis consistent with type I or II SMA who receive nusinersen, the evidence includes an open-label uncontrolled trial for which interim results have been reported. Relevant outcomes are overall survival, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Preliminary results in patients with a genetic profile consistent with type I or II SMA have shown larger improvements in motor milestones after early treatment with nusinersen compared indirectly with the natural history of SMA or healthy infants. The evidence is insufficient to determine the effects of technology on health outcomes.

Infantile-Onset or Type I SMA

For individuals who have type I (infantile-onset) SMA (symptomatic or presymptomatic) who receive nusinersen, the evidence includes 2 randomized, double-blind, controlled trial (results not yet reported for one) and a single-arm open-label study. Relevant outcomes are overall survival, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. The largest phase 3 confirmatory ENDEAR trial (N=121) showed
clinically meaningful and statistically significant improvement in motor milestones, event-free survival, and overall survival that exceeded those seen in the control group, with an acceptable safety profile. The proportion of patients, who met the primary end point responder definition of achieving motor milestones, was 51% in the nusinersen arm compared with 0% in the sham-controlled arm. Further, the hazard ratio for event-free survival was 0.53 favoring nusinersen over sham controlled. It is notable, however, that 50% of nusinersen-treated subjects did not achieve the primary end point motor milestone response. Only a small proportion of patients (6%) gained the ability to sit without assistance. On average, mean motor milestone score in nusinersen-treated patients improved by 3 points over 6 months. Given the limited data on durability of response, long-term safety, and lack of efficacy in substantial number of patients, continued risk-benefit assessment of long-term treatment with nusinersen is necessary. The open-label uncontrolled trial in presymptomatic infantile-onset SMA patients found a benefit of early treatment with nusinersen. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Type II and III SMA

For individuals who have type II or III SMA who receive nusinersen, the evidence includes 4 single-arm studies and a double-blind, randomized controlled trial. Relevant outcomes are overall survival, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Efficacy findings from single-arm studies of type II and III SMA are difficult to interpret because these trials used a wide range of nusinersen doses and lacked control arms. The largest phase 3 confirmatory CHERISH trial (N=126) showed clinically meaningful and statistically significant improvement in motor milestones (measured using Hammersmith Functional Motor Scale–Expanded scores) that exceeded those seen in the control group (difference of 5.9 points favoring nusinersen over sham control, p<0.001). The respective proportion of patients with clinically meaningful improvements in Hammersmith scores greater than 3 point was 57% vs 26% (p<0.001). Multiple secondary end points also showed a consistency in treatment effect favoring nusinersen over sham control. Given the limited data on durability of response, long-term safety, and lack of efficacy in substantial number of patients, continued risk-benefit assessment of long-term treatment with nusinersen is necessary. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Type 0 or IV SMA

For individuals who have type 0 SMA or type IV SMA who receive nusinersen, no studies were identified. Relevant outcomes are change in overall survival (type 0 only), disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. The evidence is insufficient to determine the effects of technology on health outcomes.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence has guidance in development assessing the clinical and cost effectiveness of nusinersen for treating spinal muscular atrophy. The Institute expects to release the report in November 2018.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable
MEDICARE NATIONAL COVERAGE

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02594124a</td>
<td>An Open-Label Study (SHINE) for Patients With Spinal Muscular Atrophy (SMA) Who Participated in Studies With IONIS-SMNRx</td>
<td>271</td>
<td>Feb 2020</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

REFERENCES


**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>96450</td>
<td>Chemotherapy administration, into CNS (eg, intrathecal), requiring and including spinal puncture</td>
</tr>
<tr>
<td>HCPCS</td>
<td>J2326</td>
<td>Injection, nusinersen, 0.1 mg (effective 01/01/18)</td>
</tr>
<tr>
<td></td>
<td>C9489</td>
<td>Injection, nusinersen, 0.1 mg (effective 07/01/17-12/31/17)</td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td>G12.0</td>
<td>Infantile spinal muscular atrophy, type I [Werdnig-Hoffman]</td>
</tr>
<tr>
<td></td>
<td>G12.1</td>
<td>Other inherited spinal muscular atrophy</td>
</tr>
</tbody>
</table>

Original Policy Date: March 2017
ICD-10-PCS

ICD-10-PCS codes are only used for inpatient services.

3E0R3GC

Administration, physiological systems and anatomical regions, introduction, spinal canal, percutaneous, other therapeutic substance

Type of Service

Place of Service

**POLICY HISTORY**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/21/17</td>
<td>New policy- add to Prescription Drugs section</td>
<td>Blue Cross of Idaho adopted new policy created with literature review through January 3, 2017. The use of nusinersen is considered medically necessary for patients with infantile-onset or type I SMA patients with a documented genetic diagnosis of SMA. Nusinersen is considered investigational for patients with type 0, II, III, and IV SMA. Policy becomes effective 5/01/2017.</td>
</tr>
<tr>
<td>03/29/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho annual review, no change to policy statement.</td>
</tr>
<tr>
<td>04/30/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted, effective 07/30/2018. Policy updated with literature review through February 5, 2018; references 13 and 18 added. Revisions made to the Policy section.</td>
</tr>
</tbody>
</table>