State of California—Health and Human Services Agency
Department of Health Care Services

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TO: ALL LOCAL COUNTY CALIFORNIA CHILDREN SERVICES (CCS) PROGRAM ADMINISTRATORS, MEDICAL CONSULTANTS, AND STATE INTEGRATED SYSTEMS OF CARE DIVISION (ISCD) STAFF

SUBJECT: Nusinersen (Spinraza™) – REVISED

I. PURPOSE

The purpose of this updated Numbered Letter (N.L.) is to modify the CCS Program policy regarding the authorization of nusinersen (Spinraza), as a treatment for 5q spinal muscular atrophy (SMA) for CCS Program beneficiaries with confirmed 5q spinal muscular atrophy.

II. BACKGROUND

5q SMA is an autosomal recessive neurodegenerative disorder, characterized by progressive muscle atrophy and weakness. The weakness is caused by low levels of survival motor neuron (SMN) protein with resulting degeneration of anterior horn cells in the spinal cord and motor neurons in cranial nerve nuclei of the lower brainstem. The condition is the most common genetic cause of childhood mortality, with an incidence of approximately one in 10,000 live births.

5q SMA is a single genetic disorder that results in a continuous spectrum of clinical severity; it is classified into four types based on age of onset and severity. SMA1, also known as infantile SMA, is the most common and severe type, affecting approximately 60 percent of all individuals with 5q SMA. Signs appear before six months of age in SMA1; affected individuals never sit, and the majority do not survive past two years of age. SMA2 is clinically evident later in infancy and affected individuals achieve the ability to sit but never walk; individuals with SMA2 typically survive into adulthood if provided with optimal supportive care. SMA3 comes to medical attention in childhood and SMA 4 in adulthood. Individuals with SMA3 and SMA4 have near-normal lifespan and achieve the ability to walk, though they may lose that function as the condition progresses. The motor deficits

continuously worsen in all forms of SMA, so improvement or stabilization of motor function are inconsistent with the natural history of the disease.

5q SMA is caused by the deficiency of the protein SMN, which is essential for RNA processing of gene products required for motor neuron survival. SMN is produced by two genes, SMN1 and SMN 2, both on chromosome 5q. In unaffected individuals SMN protein is almost exclusively the product of SMN1, with only a small amount from the back-up gene, SMN2. SMN2 and SMN1 encode the identical protein, but SMN2 contains a translationally silent single nucleotide polymorphism (SNP) within a splice enhancer of exon 7 that is not present in SMN1. Because of that exon 7 SNP, SMN2 transcripts are primarily spliced to produce mRNA devoid of exon 7, and unable to produce functional SMN protein. However, despite the presence of the inhibitory SNP, approximately 5-10 percent of SMN2 transcripts are spliced to contain exon 7 and produce functional full-length SMN protein.

5q SMA is inherited as a recessive disorder; all affected individuals are completely missing functional copies of SMN1, so depend on SMN2 for all SMN protein. In the general populations of all ethnic groups worldwide, 1 in 35-50 people have one chromosome 5 on which SMN1 has been deleted without producing any motor neuron abnormalities. Most individuals with 5q SMA have inherited deletions of SMN1 from each parent. Approximately 5 percent of 5q SMA patients have inherited one allele with a deletion of SMN1 and one allele with a nonsense or other null mutation of SMN1. In 10 percent of patients, one parent is not a carrier of any SMN1 mutation, but the affected offspring has a de novo mutation. Individuals with 5q SMA, having no functional SMN1 genes, rely on their copies of the SMN2 gene for all SMN protein production, which results in low levels of the SMN protein. The severity of disease varies between individuals in large part because of differences in SMN2 copy number; although most individuals have one copy of SMN2 on each chromosome 5, this is highly variable with the number of SMN2 genes ranging from zero to more than 5. Individuals with SMA who have more copies of SMN2 genes generally have less severe forms of SMA: A single SMN2 gene with no copies of SMN1 results in a patient being severely affected at birth; infants with SMA1 generally have 2 copies of SMN2; children with SMA2 usually have 3 copies of SMN2, and those with SMA3 or SMA4 have more than 3 copies.

Although SMN protein is ubiquitously expressed, its absence in 5q SMA primarily affects motor neurons, though lesser effects have been suggested to occur in other tissues.

Advances in nutrition, and pulmonary care for SMA patients have increased survivability. Without treatment targeting the mechanism of the disease, however, patients with SMA 0, 1, 2, and 3, experience steady loss of motor function and early death.

There was no Food and Drug Administration (FDA) approved disease-modifying treatment for 5q SMA until nusinersen (Spinraza) received fast track approval from the FDA in December 2016. Nusinersen is a FDA approved antisense oligonucleotide that modulates the splicing of SMN2 gene, leading to a higher percentage of transcripts containing exon 7, and consequently producing more functional SMN protein. Since all patients with 5q SMA carry and rely on their copies of SMN2 for production of SMN protein, all 5q SMA patients are treatable by nusinersen. Consequently, the FDA approved the drug for individuals of all ages with all types of 5q SMA. Studies to date indicate that the vast majority of patients treated with nusinersen have a positive response, with significant improvement or slower decline in disease progression. The time to response varies significantly, with some patients responding up to 12 months after initial treatment. Pre-symptomatic infantile onset SMA patients treated with nusinersen had higher achievement of motor milestones than symptomatic infants did in a concurrent trial, suggesting the greatest benefit with early treatment.

While nusinersen has become a critical part of SMA care, it is vital that other supportive care provided through the Special Care Center (SCC), including pulmonary services, nutrition support, and orthopedic and rehabilitation services are aggressively continued concurrently with nusinersen administration.

III. POLICY

Effective the date of this letter, nusinersen is a benefit for CCS Program clients when ALL the following criteria are met:

1. Genetic testing results demonstrate homozygous SMN1 deletion, or any combination of SMN1 deletions or other mutations that result in the functional loss of all SMN1 genes.

2. In addition to demonstrating loss of functional SMN1 genes, genetic test results should include the number of copies of SMN2.

3. The client is under the care of one of the following CCS Program approved center types: Neuromuscular SCC, Neuromusculoskeletal SCC, or pediatric rehabilitation SCC.

4. The client has the following neuromotor status:

    a. Pre-symptomatic- if the client has genetic testing demonstrating a homozygous SMN1 deletion or mutation, and </=3 copies of SMN2 or

b. Clinical signs of SMA with level of function necessary to preserve communication, for instance finger or eye movements in response to prompt by examiner.

5. Nusinersen can be safely administered intrathecally (IT). Specifically, for older clients with SMA and scoliosis, the drug may only be authorized if beneficiary:

   a. Has scoliosis without spine surgery, or

   b. Is post spine surgery with preserved window of accessibility for intrathecal injection, under fluoroscopic or ultrasound guidance if needed, or

   c. Is post spine surgery (e.g., fusion) but with surgical placement of an indwelling catheter or establishment a new window for IT accessibility.

6. The client does not have a coexisting terminal condition or a condition with which the risk of nusinersen treatment outweighs the potential benefit.

7. For initial authorization, the CCS Program approved rehabilitation, neuromuscular or neuromusculoskeletal SCC has submitted the following:

   a. The Nusinersen Request Form with all of the following information:

      (1) Patient demographics, including age of onset.

      (2) Results of genetic testing, including name of laboratory, number of copies of SMN2, and whether SMN1 sequencing was done.

      (3) Neurologic status, specifically if client is non-sitter, sitter or walker.

      (4) Results of at least one neuromotor assessment with a score used to establish a clinical baseline. The following are suggested, but any validated assessment may be used at baseline and repeated annually.

      For non-sitters:
      - CHOP Intend or
      - Hammersmith Infant Neurological Exam-Part 2 (HINE-2)

      For sitters:
      - Hammersmith Functional Motor Scale, Expanded (HFMSE) or
      - Revised Upper Limb Module (RULM)

For walkers:

- The Timed up and Go test (TUG)
- The 6 minute walk test or
- The 10-meter run/walk test

For non-ambulatory older clients:

- Revised Upper Limb Module (RULM)
- Standard muscle strength assessment

b. Copy of nusinersen prescription by CCS Program paneled neurologist or physical medicine and rehabilitation specialist at SCC where evaluation for nusinersen is completed.

c. Medical documentation of SCC visit with history and physical examination including description of plan for nusinersen administration, (e.g. in NM center or by interventional radiologist), Pulmonary status (for example hours of ventilation or BiPAP), nutrition and dietary status, with review by registered dietitian and neuromotor assessment.

d. Genetic laboratory confirmation of diagnosis.

e. At least one neuromotor assessment with a score used to establish a clinical baseline. The assessment can be any listed in III (7) (a) (4) or any other validated assessment that would be completed at baseline and repeated annually.

8. For reauthorization, the CCS Program approved rehabilitation, neuromuscular or neuromusculoskeletal SCC has submitted the following:

a. Date of initiation of nusinersen.

b. SCC progress notes with specific description of change in neuromotor status since initiation of medication and any drug-related toxicity.

c. Progress notes that document any observed clinical change in neuromotor status every six months.

d. Neuromotor assessment, completed at the SCC every 12 months, which demonstrates improvement or lack of deterioration since initiation of nusinersen, with positive response to medication documented by comparing scores to the results prior to medication.

e. Requests for reauthorization in cases in which there is clinical decline, or in cases in which the patient's deficits prevent completion of any of the standardized assessments will be reviewed by the ISCD medical director or designee.

9. The request is for the FDA approved dosage only, with the approved loading and maintenance schedules.

   a. Nusinersen is a 12 mg suspension, to be administered intrathecally.

   b. The nusinersen treatment schedule consists of four loading doses of 12mg, at days 1, 15, 29, 59, and maintenance doses every 4 months thereafter.

IV. POLICY IMPLEMENTATION

A. Nusinersen requires separate authorizations for outpatient administration and pharmacy dispensing.

   1. Requesting CCS Program providers must submit the following items to their beneficiaries' local CCS Program county office or Dependent County Regional Office:

      a. CCS Program Service Authorization Request (SAR) for

         (1) For dates of service from July 1 to December 31, 2017, use HCPCS code, C9489, to SCC if the SCC will be supplying the drug, one unit of C9489=injection, nusinersen, 0.1mg. Beginning with dates of service beginning January 1, 2018, use HCPCS code, J2326. One unit of J2326 = injection, nusinersen, 0.1mg.

         (2) NDC if a specialty pharmacy will supply the drug

         (3) SCG02 or SCG01 with additional codes needed for procedures and equipment related to nusinersen administration.

      b. Nusinersen Request Form, completed by the CCS Program approved SCC, with neuromotor assessment scores every 12 months and summary of changes in neuromotor status every six months.

      c. Supporting documentation described in III (7) and III (8) above.

The request will be for SCG02 or SCG01 with additional codes needed for procedures and equipment related to nusinersen administration.

The HCPCS code C9489 or J2326, as described in A(1)(a)(1), will be requested by the SCC, ONLY if pharmacy is NOT requesting authorization for the client. If dates of service overlap the applicable dates for using C9489 or J2326, it is highly recommended that separate SARs be issued for each HCPCS code.

In most cases, the specialty pharmacy contracted to provide nusinersen will submit a request for authorization of the medication. This request will be for NDC 64406005801.

2. When the County CCS Program determines that the requests and documentation submitted by the center and pharmacy are complete, the county will pend a Service Authorization Request (SAR) to a specialty pharmacy or to a SCC for drug administration, and forward the completed Nusinersen Request Form and supporting documentation to the Nusinersen e-mail inbox:

   CCS_Operations@dhcs.ca.gov or via secure Right fax number: (916) 440-5768.

3. The State CCS Program office will issue initial authorization for a period of six months or until the end of program eligibility period. The initial authorization shall cover up to five doses depending on the length of the authorization period and history of prior doses received.

4. Extension of the authorization shall be granted every six months following review of documentation described above unless there are significant adverse effects or change in eligibility. After one year of treatment, further authorizations will be done by the local county CCS Program or Dependent County Regional Office.

5. Minor SAR changes, such as changes to SAR dates to align with SAR period may be completed by county without state review.

B. All requests shall be reviewed by the ISCD Medical Director or designee before authorization of nusinersen.

C. Institutional providers purchasing and administering nusinersen must obtain SAR approval and bill with the appropriate HCPCS code, depending on date of service, as described in A(1)(a)(1).

Currently, the manufacturer has authorized one specialty pharmacy to supply/dispense nusinersen. The pharmacy may obtain a SAR and bill by NDC if the administering facility is not directly purchasing the drug. The authorized pharmacy provider is contracted by the manufacturer to deliver directly to the facility administering nusinersen on the day of administration.

D. Exceptions will be reviewed on a case-by-case basis by the State CCS Medical Consultant.

If you have any questions regarding this policy, please contact Jill Abramson, M.D., MPH by telephone at (916) 327-2108 or via email at jill.abramson@dhcs.ca.gov

Sincerely,

ORIGINAL SIGNED BY

Sarah Eberhardt-Rios, Division Chief
Integrated Systems of Care Division

ATTACHMENT: Nusinersen Request Form

Nusinersen Request Form

Full Name		CCS Case #	Date Completed
County		Age	Nusinersen applicable 5q mutation (yes/no)
SMA Type			
SMN1 sequencing (and laboratory name) y/n		Number of SMN2 copies (and laboratory name)	
Age of onset			
Other medical condition			
Neurologic status (circle one): Non-sitter, Sitter, Walker			
Method of administration (LP, Ommaya, Window)			
I. Clinical Baseline Prior to Loading Doses – center to complete at least one assessment			
CHOP Intend total score, non-sitter			Date Completed
Hammersmith Infant Neurological Exam-Part 2 (HINE-2) total score, non-sitter			Date Completed
Hammersmith Functional Motor Scale, Expanded (HFMSE) total score, sitter			Date Completed
6-minute walk test (6MWT), walker			Date Completed
10 meter walk/run test (10MWR), walker			Date Completed
Timed Up and Go test (TUG), walker			Date Completed
Revised Upper Limb Module (RULM)			Date Completed
Other neuromotor assessment			Date Completed
Notes			
II. Request For Authorization for Maintenance Doses – center to complete the assessment used for baseline			
CHOP Intend total score, non-sitter			Date Completed
Hammersmith Infant Neurological Exam-Part 2 (HINE-2) total score, non-sitter			Date Completed
Hammersmith Functional Motor Scale, Expanded (HFMSE) total score, sitter			Date Completed
6-minute walk test (6MWT), walker			Date Completed
10 meter walk/run test (10MWR), walker			Date Completed
Timed Up and Go test (TUG), walker			Date Completed
Revised Upper Limb Module (RULM)			Date Completed
Other neuromotor assessment			Date Completed
Dates of nusinersen administration including next dose: Change in neuromotor status on Nusinersen in past 6 months			
Adverse effects of Nusinersen			
Form Completed By (Name/Title):			Date Completed
Special Care Facility Name:			
To be completed by CCS staff			
Approved ☐ Denied ☐ Reason for Denial:			Date:
Reviewed By (ISCD staff)			