TEMPLATE

Letter of Medical Necessity

For Medical Procedures Associated with the Administration of AMONDYS 45

Date:

[Insert Name of Medical Director] RE: Patient Name [_____]

[Insurance Company] Policy Number [_____]

[Address] Claim Number [_____]

[City, State, Zip]

Dear [Insurance Company]:

I am writing this letter of medical necessity to provide information related to the treatment of [insert patient name] with AMONDYS 45^{tm}, a drug for the treatment of Duchenne muscular dystrophy patients with specific mutations amenable to skipping exon 45. The FDA approved this therapy under accelerated approval based on an increase in dystrophin in skeletal muscle observed in patients.[1] The FDA's broad label[2] presents the possibility of slowing the progression of disease in Duchenne patients amenable to skipping exon 45.

I would like to provide the following information about the potential benefit of AMONDYS 45 in Duchenne patients:

1. Duchenne pathophysiology

Duchenne muscular dystrophy is caused by mutations in the dystrophin gene. This gene is an x-linked genetic disorder characterized by the progressive loss of skeletal muscle and degeneration, primarily in boys. It affects one out of 5000 live male births in the US.[3,4] The average age at diagnosis is approximately five years[5,] but delays in motor milestones (such as sitting, standing independently, climbing, and walking) occur much earlier.[6] With 79 exons, the dystrophin gene is one of the largest known human genes. Its size and error-prone areas (hotspots) make it more likely to have mutations, which can be deletions or duplications of exons, small missing or extra pieces, or tiny substitutions, in genetic code. The most frequent mutation is a deletion. Deletions may result in either an out of frame mutation, closing the reading frame and producing no dystrophin, or an in frame mutation, resulting in a truncated dystrophin. Exon skipping is a strategy involving splice-switching oligomers, changing an out of frame mutation (with no dystrophin production) to an in frame mutation (with truncated dystrophin production).[7] 8% of all Duchenne patients have a genetic deletion amenable to skipping exon 45.

Dystrophin is located beneath the sarcolemma, and functions to connect the subsarcolemmal cytoskeleton to the sarcolemma.[8] A loss of dystrophin in muscle results in inflammation, muscle degeneration and replacement of muscle with fibroadipose (fat and fibrotic) tissue. The primary symptoms of Duchenne muscular dystrophy are caused by a lack of dystrophin in the muscle. Children with Duchenne lose the ability to walk independently and most become reliant on wheelchairs for mobility by the age of 13.[8] Most individuals with Duchenne experience serious respiratory, orthopedic, and cardiac complications. By the age of 18, the majority of patients require ventilation

support at night.[9] The average life expectancy is approximately 30 years of age, with respiratory complications and cardiomyopathy being common causes of death.[9] Standard medical management of Duchenne requires attention to the use of corticosteroids as well as respiratory, cardiac, orthopedic, and rehabilitative interventions aimed at the sequela that progressively worsen throughout the lifespan of Duchenne.[9] Corticosteroids slow the progression of muscle weakness and delay some of the complications of the disease, but they do not treat or correct the underlying causes of Duchenne.

2. Description of AMONDYS 45

AMONDYS 45 (Casimersen) is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the five-membered ribofuranosyl rings found in natural DNA and RNA are replaced by a six-membered morpholino ring. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in natural DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). AMONDYS 45 contains 22 linked subunits. The sequence of bases from the 5' end to 3' end is CAATGCCATCCTGGAGTTCCTG. The molecular formula of AMONDYS 45 is C268 H424 N124 O95 P22 and the molecular weight is 7584.5 daltons.

3. Mechanism of action of AMONDYS 45

AMONDYS 45 (Casimersen) is designed to bind to exon 45 of dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 45 skipping. Exon 45 skipping is intended to allow for production of an internally truncated dystrophin protein in patients with genetic mutations that are amenable to exon 45 skipping.

4. Dosing Schedule of AMONDYS 45[2]

Dosing for AMONDYS 45 is 30 milligrams per kilogram of body weight once weekly.
AMONDYS 45 is supplied in single dose vials containing 100mg or 500 mg of drug (50mg/mL).

5. Administration of AMONDYS 45[2]

AMONDYS 45 is given weekly by intravenous (IV) infusion, via either peripheral or central venous access.

6. Rationale for Treatment

Advances in medical management have significantly improved life expectancy and quality of life. The use of corticosteroids has pushed the age at loss of ambulation to around 13 years old, demonstrating delayed decline of lower limb skeletal muscle. However, corticosteroids do not treat the underlying cause of the disease. AMONDYS 45 is intended to allow for production of an internally truncated but functional dystrophin protein. I believe AMONDYS 45 supplied to my patient will help to preserve muscle, delaying loss of function.

7. Summary of Patient's History [You may want to include]:

- ☐ Chart notes
- ☐ Genetic tests
- ☐ Copy of the patient's insurance cards
- ☐ FDA Approval Letter
- ☐ Prescribing information
- ☐ Recent medical articles
- ☐ Letters from other specialists treating the patient such as cardiologists, pulmonologists and physical and occupational therapists
- ☐ Patient's psychological factors that are relevant to your chosen treatment

☐ Information to educate Medical Director or Pharmacy Director who is not familiar with the disease or treatment

8. Patient's prognoses

- Summary of your professional opinion of the patient's likely prognoses without treatment with AMONDYS 45

9. Concluding Remarks

Based on the clinical data available to date, it is my medical opinion that initiating treatment of **[patient name]** with AMONDYS 45 is medically appropriate and necessary and the procedures required for its administration should be a covered and reimbursed service. Below, this letter outlines **[patient name's]** medical history, prognoses, and the rationale for treatment with AMONDYS 45 **[to be completed by physician based on patient medical history and prognosis**]. I am requesting an expedited review of this case due to the fatality of this disease.

HCP to insert information relevant to particular case (e.g., Given the patient's history, his/her current condition, lack of treatment options for Duchenne and the emerging data of the effects of AMONDYS 45 in Duchenne patients amenable to skipping exon 45.

Please call my office at **[insert telephone number]** if I can provide you with any additional information. I look forward to receiving your timely response and approval of this claim.

Sincerely,

[Insert Doctor name and

Participating provider number]

References

[1] Center for Drug Evaluation and Research Application Number: 213026orig1s000 Retrieved from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213026Orig1s000MedR.pdf
[2] Casimersen (AMONDYS 45) FDA label. Retrieved from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213026lbl.pdf
[3] Mendell JR, Shilling C, Leslie ND, et al. Evidence Based Path to Newborn Screening for Duchenne Muscular Dystrophy. Ann Neurol 2012;71:304-313.
[4] Mah JK, Korngut L, Dykeman J, Day L, Pringsheim T, Jette N. A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy. 2014;24:482-491.
[5] Ciafaloni E, Fox DJ, Pandya S, Westfield CP, Puzhankara S, Romitti PA, et al. Delayed diagnosis in Duchenne muscular dystrophy: data from the muscular dystrophy surveillance, tracking, and research network (MD-STARnet). J Pediatr 2009;155:380-385.
[6] Bushby K, Birnkrant DJ, et al. *Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management* Lancet Neurol 2018
[8]Bello L, Gordish-Dressman H1, Morgenroth LP1, Henricson EK1, Duong T1, Hoffman EP1, Cnaan A1, McDonald CM2; CINRG Investigators. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. Neurology. 2015
[9]Birnkrant DJ, Bushby K, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management Lancet Neurology 2018