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Subject: Exon-Skipping Therapy for Duchenne Muscular Dystrophy

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Muscular dystrophy includes a group of genetic disorders that cause muscle weakness and progressive disability. Duchenne muscular dystrophy (DMD) is the most common and progresses most rapidly. This X-linked recessive disorder is caused by mutations (mainly deletions) in the dystrophin gene that lead to an absence or defect in the dystrophin protein.

Dystrophin is thought to maintain the structural integrity of the muscle cell membrane by connecting the cytoskeleton to the underlying extracellular matrix and acting as a scaffold for several molecules that also contribute to normal muscle physiology. Absence of dystrophin leads to mitochondrial dysfunction and damage, with inflammatory processes also appearing to contribute to muscle pathology. Muscle fibers ultimately undergo necrosis with replacement by adipose and connective tissue. Principal disease manifestations include progressive degeneration of skeletal and cardiac muscle, leading to loss of physical function in childhood and adolescence with premature death from respiratory and/or cardiac failure in the second to fourth decade.

As males have only one X chromosome, and thus one single copy of the dystrophin gene, they have a much higher probability of developing DMD. A small number of females are also affected but remain asymptomatic and only rarely present with a mild form of the disease. DMD has an estimated incidence of 1 in 3,500 male births. Available data suggests around 83% of DMD patients have genotypes amenable to exon skipping, and that 13% of DMD patients have genotypes that are amenable to exon 51 skipping.

Treatment options for DMD predominantly focus on management of symptoms and secondary complications. Glucocorticoids are the only pharmacological treatments that have been shown to improve skeletal muscle strength and function in reproducible randomized controlled trials; they also

reduce the risk of scoliosis, stabilize pulmonary function, and may also improve cardiac function. Current guidelines recommend initiation of glucocorticoids (such as prednisolone) once patients reach a plateau of motor skill development, generally at age 4-6 years, but prior to onset of motor decline.

Other pharmacologic therapies for DMD are primarily aimed at the management of comorbidities such as cardiomyopathy, osteoporosis, pain management, and respiratory failure. These treatment options include angiotensin-converting-enzyme (ACE) inhibitors, beta-blockers, calcium and vitamin D supplements, muscle relaxants, and non-steroidal anti-inflammatory drugs.

Eteplirsen (Exondys 51®)

Eteplirsen was approved by the U.S. Food and Drug Administration (FDA) in September 2016 for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication was approved under accelerated approval using a surrogate endpoint: increase in dystrophin in skeletal muscle observed in some patients. The FDA label includes the following statement, "Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials." Prior to FDA approval, the Peripheral and Central Nervous System Drugs Advisory Committee of the FDA held a meeting and voted against approval of Eteplirsen as treatment for DMD. Much uncertainty exists regarding whether the small observed increase in dystrophin will confer a clinically meaningful benefit.

Eteplirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) class that selectively binds to exon 51 of the dystrophin pre-messenger ribonucleic acid (pre-mRNA). This causes the exon to be skipped and prevents that part of the code from being read during mRNA processing, thereby repairing the mutated reading frame in the mRNA coding sequence in patients with a deletion in exons 45-50, 47-50, 48-50, 49-50, 50, 52, or 52-63 of this gene. In doing so, eteplirsen enables the production of an internally truncated, yet functional, dystrophin protein.

Eteplirsen was evaluated in several clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Study 201 was a single-center, double-blind, placebo-controlled study in 12 patients with DMD. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (4 patients per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. These patients have continued to receive eteplirsen for more than 4 years. This continuous study is referred to as Study 201/202.

In Study 201, patients were randomized to receive weekly infusions of eteplirsen (30 mg/kg, n=4); eteplirsen (50 mg/kg, n=4), or placebo (n=4) for 24 weeks. The primary endpoint was dystrophin production; a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 9.4 years, a mean 6-minute walk distance (6MWD) at baseline of 363 meters and were on a stable dose of corticosteroids for at least 6 months. There was no significant difference in change in 6MWD between patients treated with eteplirsen and those treated with placebo.

Patients who participated in Study 201/202 were compared to an external control group. The primary clinical efficacy outcome measure was the 6MWT. Eleven patients in Study 201/202 had a muscle biopsy after 180 weeks of treatment with eteplirsen, which was analyzed for dystrophin protein level by Western blot. Study 201/202 failed to provide evidence of a clinical benefit of eteplirsen compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with eteplirsen was 0.93% of the dystrophin level in healthy subjects. Baseline measurements were not available.

Study 301 is an externally controlled study where all patients are receiving open label eteplirsen, 30 mg/kg, by weekly infusion. The study is ongoing and still accruing patients. Interim data were obtained from patients in this study and the FDA’s approval was based on the unpublished results of Study 301.

In Study 301, 13 patients were treated with open label eteplirsen (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. Patients had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least 6 months. Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with eteplirsen (p < 0.05). The median increase after 48 weeks was 0.1%. It should be noted that the clinical significance of this is unknown.

Individual patient dystrophin levels from Study 301 are shown in Table 1.

Table 1. Dystrophin Expression in Individual Patients (Study 301)

Patient	Western Blot % Normal Dystrophin		
	Baseline	Week 48	Change from Baseline
1	0.13	0.26	0.13
2	0.35	0.36	0.01
3	0.06	0.37	0.31
4	0.04	0.10	0.06
5	0.17	1.02	0.85
6	0.37	0.30	-0.07
7	0.17	0.42	0.25
8	0.24	1.57	1.33
9	0.11	0.12	0.01
10	0.05	0.47	0.43
11	0.02	0.09	0.07
12	0.18	0.21	0.03
Mean	0.16	0.44	0.28; p=0.008

In the 88 patients who received ≥30 mg/kg/week of eteplirsen for up to 208 weeks in clinical studies, the following events were reported in ≥10% of patients and occurred more frequently than on the same dose in Study 201: vomiting, contusion, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection. There have been reports of transient erythema, facial flushing, and elevated temperature occurring on days of eteplirsen infusion.

There is an ongoing Phase III confirmatory trial evaluating the efficacy of eteplirsen in DMD with a target enrollment of 160 patients. The estimated completion date is January 2019.

Golodirsen (Vyondys 53®)

Golodirsen was approved by the FDA in December 2019 for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication was approved under accelerated approval using a surrogate endpoint: increase in dystrophin in skeletal muscle observed in some patients. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. Much uncertainty exists regarding whether the small observed increase in dystrophin will confer a clinically meaningful benefit.

Golodirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) class that selectively binds to exon 53 of the dystrophin pre-mRNA. This causes the exon to be skipped and prevents that part of the code from being read during mRNA processing, thereby repairing the mutated reading frame in the mRNA coding sequence. In doing so, golodirsen enables the production of an internally truncated, yet functional, dystrophin protein.

Golodirsen was evaluated in patients aged 6 to 15 years who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. Study 4053-101 (NCT02310906) two-part study with part 1 designed as a double-blind, placebo-controlled, dose-titration study in 12 patients. Part 2 was a 168 week, open-label study assessing the safety and efficacy of golodirsen 30 mg/kg/week in the 12 patients enrolled in part 1 plus 13 additional patients.

The primary endpoint was change in dystrophin production from baseline to week 48. A clinical outcome measure, the change in 6MWT from baseline to week 144, was also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 8 years and were on a stable dose of corticosteroids for at least 6 months.

Dystrophin levels in muscle tissue were assessed by Western blot. In the 25 patients enrolled in the clinical trial, mean dystrophin levels increased from 0.10% (SD 0.07) of normal at baseline to 1.02% (SD 1.03) of normal by Week 48 of part 2, with a mean change in dystrophin of 0.92% (SD 1.01) of normal levels ($p < 0.001$); the median change from baseline was 0.88%. It should be noted that the clinical significance of this is unknown.

Individual patient dystrophin levels from the study are shown in Table 2.

Table 2. Dystrophin Expression in Individual Patients (Study 4053-101)

Patient	Western Blot % Normal Dystrophin		
	Baseline	Week 48	Change from Baseline
1	0.08	0.09	0.01
2	0.11	0.11	0.01
3	0.21	0.22	0.01
4	0.05	0.12	0.08
5	0.03	0.12	0.09

6	0.06	0.14	0.09
7	0.12	0.37	0.25
8	0.11	1.06	0.95
9	0.06	0.54	0.48
10	0.05	0.97	0.92
11	0.06	1.55	1.49
12	0.07	1.91	1.84
13	0.10	3.25	3.15
14	0.22	0.28	0.06
15	0.14	0.21	0.07
16	0.05	0.42	0.37
17	0.07	1.03	0.97
18	0.02	1.57	1.55
19	0.12	1.17	1.05
20	0.03	1.72	1.69
21	0.11	1.77	1.66
22	0.31	4.30	3.99
23	0.11	0.36	0.25
24	0.03	0.91	0.88
25	0.07	1.29	1.22
Mean	0.10	1.02	0.92; p<0.001

There is an ongoing Phase III confirmatory trial (ESSENCE) evaluating the efficacy of golodirsen in DMD.

Viltolarsen (Vilteps[®])

Viltolarsen was approved by the FDA in August 2020 for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication was approved under accelerated approval using a surrogate endpoint: increase in dystrophin in skeletal muscle observed in some patients. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. Much uncertainty exists regarding whether the small observed increase in dystrophin will confer a clinically meaningful benefit.

Viltolarsen is an antisense oligonucleotide that selectively binds to exon 53 of the dystrophin pre-mRNA. This causes the exon to be skipped and prevents that part of the code from being read during mRNA processing, thereby repairing the mutated reading frame in the mRNA coding sequence. In doing so, golodirsen enables the production of an internally truncated, yet functional, dystrophin protein.

Viltolarsen was evaluated in patients aged 4 to 10 years who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. Study 1 (NCT02740972) was a multicenter, 2-period, dose-finding study. During the initial period (first 4 weeks) of Study 1, patients were randomized (double blind) to viltolarsen or placebo. All patients then received 20 weeks of open label viltolarsen 40 mg/kg once weekly (0.5 times the recommended dosage) (N=8) or 80 mg/kg once weekly (N=8). Study 1 enrolled ambulatory male patients 4 years to less than 10 years of age (median age 7 years) on a stable corticosteroid regimen for at least 3 months.

Efficacy was assessed based on change from baseline in dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 25. Muscle biopsies (left or right biceps brachii) were collected from patients at baseline and following 24 weeks of viltolarsen treatment and analyzed for dystrophin protein level by Western blot normalized to myosin heavy chain (primary endpoint) and mass spectrometry (secondary endpoint).

In patients who received viltolarsen 80 mg/kg once weekly, mean dystrophin levels increased from 0.6% (SD 0.8) of normal at baseline to 5.9% (SD 4.5) of normal by Week 25, with a mean change in dystrophin of 5.3% (SD 4.5) of normal levels ($p=0.01$) as assessed by validated Western blot (normalized to myosin heavy chain); the median change from baseline was 3.8%. All patients demonstrated an increase in dystrophin levels over their baseline values. As assessed by mass spectrometry (normalized to filamin C), mean dystrophin levels increased from 0.6% (SD 0.2) of normal at baseline to 4.2% (SD 3.7) of normal by Week 25, with a mean change in dystrophin of 3.7% (SD 3.8) of normal levels (nominal $p=0.03$, not adjusted for multiple comparisons); the median change from baseline was 1.9%.

Individual patient dystrophin levels from the study are shown in Table 3.

Table 3: Dystrophin Expression in Individual Patients (Study 1)

Patient	Western Blot % Normal Dystrophin		
	Baseline	Week 25	Change from Baseline
1	0.46	1.14	0.69
2	0.40	3.97	3.57
3	0.46	2.97	2.51
4	0.09	10.40	10.31
5	0.51	14.42	13.91
6	2.61	7.40	4.79
7	0.43	3.06	2.63
8	0.09	4.07	3.98
Mean	0.6	5.9	5.3; $p=0.01$

Casimersen (Amondys 45®)

Casimersen was approved by the FDA in February 2021 for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping. This indication was approved under accelerated approval using a surrogate endpoint: increase in dystrophin in skeletal muscle observed in some patients. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. Much uncertainty exists regarding whether the small observed increase in dystrophin will confer a clinically meaningful benefit.

Casimersen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) class. Casimersen binds to exon 45 of the dystrophin pre-mRNA. This causes the exon to be skipped and prevents that part of the code from being read during mRNA processing, thereby repairing the mutated reading frame in the mRNA coding sequence. In doing so, casimersen enables the production of an internally truncated, yet functional, dystrophin protein.

Casimersen was evaluated in ambulatory patients aged 7 to 13 years who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping. Study 1 (NCT02500381) is an ongoing, double-blind, placebo-controlled trial. Patients were required to be on a stable dose of corticosteroids for at least 24 weeks. Following the 96-week double-blind period, all patients transition to an additional 48 week open-label treatment period.

The primary endpoint was change from baseline in total distance walked during 6MWT at week 96. Secondary outcomes include change from baseline in distance walked during 6MWT at week 144, change from baseline in dystrophin production and intensity at week 48 or 96, ability to rise independently from the floor, time to loss of ambulation, change from baseline in NSAA score at week 96 and week 144, and change from baseline in FVC% predicted at week 96 and 144.

Interim results from 43 patients (n=27 casimersen; n=16 placebo) who had a muscle biopsy at week 48 of the double-blind period are presented in table 4.

Table 4. Muscle Biopsy Interim Results (Study 1)

	Placebo	Casimersen
Dystrophin by Sarepta Western blot	n=16	n=27
Baseline Mean (SD)	0.54 (0.79)	0.93 (1.67)
Week 48 Mean (SD)	0.76 (1.15)	1.74 (1.97)
Change from Baseline Mean (SD)	0.22 (0.49)	0.81 (0.70)
p-value Change from Baseline to Week 48	0.09	<0.001
Between group mean difference	0.59	
p-value between groups	p=0.004	

There is an ongoing Phase III confirmatory trial (ESSENCE) evaluating the efficacy of casimersen in DMD.

POSITION STATEMENT:

Initiation of exon-skipping therapy for Duchenne muscular dystrophy (DMD) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Indication for use is treatment of Duchenne muscular dystrophy (DMD)
2. Member has a mutation of the DMD gene that is amenable to exon-skipping therapy as described in the product's "Indications and Usage" section of the FDA-approved prescribing information (or package insert) – laboratory documentation must be provided (see Table 5 for product specific requirements)
3. Member is ambulatory (e.g., able to walk with assistance, not wheelchair dependent) – documentation from the medical record must be provided
4. Member has a recent (within four weeks of request) pre-treatment 6-Minute Walk Time of at least 300 meters while walking independently (e.g., without assist, cane, walker, wheelchair) – documentation from the medical record must be provided
5. Member's baseline muscle strength prior to initial treatment is established with one of the following exams:
 - a. 6-Minute Walk Test (6MWT)

- b. North Star Ambulatory Assessment (NSAA)
- c. Motor Function Measure (MFM)

NOTE: Submission of muscle strength is not required for initial approval, but will be required upon request for continuation of therapy

- 6. Requested product will not be used concomitantly with another exon-skipping therapy for DMD
- 7. Treatment is prescribed by a board certified (or board eligible) neurologist
- 8. Member is not enrolled in a clinical trial to receive an experimental drug or gene therapy for DMD
- 9. Dose does not exceed maximum FDA-approved dose and frequency (see Table 5 for product specific requirements)

Approval duration: 6 months

Continuation of exon-skipping therapy for DMD **meets the definition of medical necessity** when **ALL** of the following criteria are met:

- 1. Authorization/reauthorization has been previously approved by Florida Blue in the past two years for treatment of Duchenne muscular dystrophy (DMD), OR the member has previously met all indication-specific initiation criteria
- 2. Member has a mutation of the DMD gene that is amenable to exon-skipping therapy as described in the product's "Indications and Usage" section of the FDA-approved prescribing information (or package insert) – laboratory documentation must be provided (see Table 5 for product specific requirements)
- 3. Member has demonstrated a beneficial response in DMD-associated symptoms – documentation from medical record must be provided
- 4. Member is ambulatory (e.g., able to walk with assistance, not wheelchair dependent) – documentation from the medical record must be provided
- 5. Member has improved or maintained a previous improvement in muscle strength as demonstrated by recent (within 60 days of request) results from one of the following exams – documentation from the medical record must be provided
 - a. 6-Minute Walk Test (6MWT)
 - b. North Star Ambulatory Assessment (NSAA)
 - c. Motor Function Measure (MFM)
- 6. Requested product will not be used concomitantly with another exon-skipping therapy for DMD
- 7. Treatment is prescribed by a board certified (or board eligible) neurologist
- 8. Member is not enrolled in a clinical trial to receive an experimental drug or gene therapy for DMD
- 9. Dose does not exceed maximum FDA-approved dose and frequency (see Table 5 for product specific requirements)

Approval duration: 6 months

Table 5**Criteria for use of exon-skipping therapy for DMD**

Product	Required Criteria (ALL must be met)
Casimersen <i>Amondys 45</i>	<ol style="list-style-type: none"> 1. Member has a mutation of the DMD gene amenable to exon 45 skipping – laboratory documentation must be provided 2. Dose does not exceed 30 mg/kg once weekly
Eteplirsen <i>Exondys 51</i>	<ol style="list-style-type: none"> 1. Member has a mutation of the DMD gene amenable to exon 51 skipping – laboratory documentation must be provided 2. Dose does not exceed 30 mg/kg once weekly
Golodirsen <i>Vyondys 53</i>	<ol style="list-style-type: none"> 1. Member has a mutation of the DMD gene amenable to exon 53 skipping – laboratory documentation must be provided 2. Dose does not exceed 30 mg/kg once weekly
Viltolarsen <i>Viltepso</i>	<ol style="list-style-type: none"> 1. Member has a mutation of the DMD gene amenable to exon 53 skipping – laboratory documentation must be provided 2. Dose does not exceed 80 mg/kg once weekly

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Casimersen
 - 30 milligrams per kilogram of body weight once weekly
 - Administer as an intravenous infusion over 35 to 60 minutes
- Eteplirsen
 - 30 milligrams per kilogram of body weight once weekly
 - Administer as an intravenous infusion over 35 to 60 minutes
- Golodirsen
 - 30 milligrams per kilogram of body weight once weekly
 - Administer as an intravenous infusion over 35 to 60 minutes
- Viltolarsen
 - 80 milligrams per kilogram of body weight once weekly
 - Administer as an intravenous infusion over 60 minutes

Dose Adjustments

- Casimersen

- None
- Eteplirsen
 - None
- Golodirsen
 - None
- Viltolarsen
 - None

Drug Availability

- Casimersen
 - 100 mg/2 mL (50 mg/mL) in single-dose vial
- Eteplirsen
 - 100 mg/2 mL (50 mg/mL) in single-dose vial
 - 500 mg/10 mL (50 mg/mL) in single-dose vial
- Golodirsen
 - 100 mg/2 mL (50 mg/mL) in single-dose vial
- Viltolarsen
 - 250 mg/5 mL (50 mg/mL) in a single-dose vial

PRECAUTIONS:

Boxed Warning

- Casimersen
 - None
- Eteplirsen
 - None
- Golodirsen
 - None
- Viltolarsen
 - None

Contraindications

- Casimersen
 - None
- Eteplirsen
 - None
- Golodirsen
 - None
- Viltolarsen

- None

Precautions/Warnings

- Casimersen
 - Kidney toxicity
- Eteplirsen
 - Hypersensitivity reactions
- Golodirsen
 - Hypersensitivity reactions
 - Kidney toxicity
- Viltolarsen
 - Kidney toxicity

BILLING/CODING INFORMATION:

HCPCS Coding

J1426	Injection, casimersen, 10 mg
J1427	Injection, viltolarsen, 10 mg
J1428	Injection, eteplirsen, 10 mg
J1429	Injection, golodirsen, 10 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

G71.01	Duchenne or Becker muscular dystrophy
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REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

DEFINITIONS:

6 minute walk test: assesses distance walked over 6 minutes as a sub-maximal test of aerobic capacity/endurance

9 Hole Peg Test: a brief, standardized quantitative test of upper extremity function

Maximum Voluntary Isometric Contraction Test: assesses muscle strength

North Star Ambulatory Assessment: a functional scale designed for ambulant boys affected by DMD

RELATED GUIDELINES:

None

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/12/21.

GUIDELINE UPDATE INFORMATION:

04/01/21	New Medical Coverage Guideline.
07/01/21	Added HCPCS codes J3490 and C9078 and deleted code C9071.
10/01/21	Revision: Added HCPCS code J1426 and deleted codes J3490 and C9078.
12/15/22	Revised position statement.