Medical Policy
Gene Therapies for Duchenne Muscular Dystrophy

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Policy Number: 022
BCBSA Reference Number: N/A
NCD/LCD: N/A

Related Policies
Prior Authorization Request Form for Elevidys™ (delandistrogene moxeparvovec-rokl), #025

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Prior Authorization Request Form: Elevidys (delandistrogene moxeparvovec-rokl)
*This form must be completed and faxed to: Medical and Surgical: 1-888-973-0726; Medicare Advantage: 1-800-447-2994.

Prior Authorization Request Form for Elevidys (delandistrogene moxeparvovec-rokl), #025

Delandistrogene moxeparvovec-rokl (Elevidys)
Delandistrogene moxeparvovec-rokl (Elevidys) may be considered MEDICALLY NECESSARY for the treatment of Duchenne muscular dystrophy (DMD) in patients who meet ALL of the following criteria:
1. Diagnosis of DMD by or in consultation with a pediatric neuromuscular specialist in DMD with:
   a. A confirmed mutation in the DMD gene; AND
   b. Mutation is not a deletion in exon 8 and/or 9; AND
2. Elevidys is prescribed by or in consultation with a pediatric neuromuscular specialist in DMD; AND
3. Patient is 4 - 5 years old; AND
4. Patient is ambulatory without need of assistive devices (e.g., cane, walker, wheelchair, side-by-side assistance, etc.) as determined by medical records or physician attestation; AND
5. Patient does not have an anti-AAVrh74 total binding antibody titer ≥ 1:400; AND
6. Patient is on a corticosteroid regimen:
   a. Stable corticosteroid regimen defined as ≥ 12 weeks prior to screening for Elevidys infusion and following infusion; OR
   b. Corticosteroid is not medically/clinically appropriate as per managing provider's recommendations; AND
7. Patient has not previously received a gene therapy with Elevidys in their lifetime; AND
8. Prescriber attestation patient will not receive any exon skipping therapies for DMD [e.g., Amondys (casimersen), Exondys 51 (eteplirsen), Viltepso (viltolarsen), Vyondys 53 (golodirsen)] concomitantly or following treatment with Elevidys; **AND**

9. Prescriber will assess liver function, platelets, and troponin-I levels prior to Elevidys infusion.

**Note:** Pre-existing active coverage authorizations for EXONDYS 51, VYONDYS 53, and AMONDYS 45, will not be prematurely discontinued at the time of Elevidys approval as long as the exon-skipping drugs continue to be deemed medically necessary by the Healthcare Provider, and until the patient receives treatment with delandistrogene moexparpovec-rokl.

**Coverage Limitation:**
Authorization will be for no more than one lifetime treatment.
Length of authorization of 180 days from date of approval or up to 6 years of age, which ever comes first.

**Note:** The safety and effectiveness of repeat administration of delandistrogene moexparpovec-rokl has not been evaluated. Therefore, coverage will be limited to once per lifetime.

The use of delandistrogene moexparpovec-rokl that does not meet the criteria as indicated in this policy is considered **EXPERIMENTAL/INVESTIGATIONAL** and therefore non-covered because the safety and/or effectiveness of this service cannot be established by the available published peer-reviewed literature.

Delandistrogene moexparpovec-rokl is considered **INVESTIGATIONAL** when the above criteria are not met.

Repeat treatment of Delandistrogene moexparpovec-rokl is considered **INVESTIGATIONAL**.

Delandistrogene moexparpovec-rokl is considered **INVESTIGATIONAL** for all other indications.

**Policy Guidelines**

**Recommended Dose:** The minimum recommended dose is \(1.33 \times 10^{14}\) vector genomes (vg) per kg of body weight.

**Dosing Limits:** 1 injection per lifetime

**Other Considerations:**
Due to the risk of acute liver injury, liver function should be monitored before Elevidys infusion, with a weekly monitoring for the first 3 months post infusion. Monitoring should continue until results are unremarkable. Consultation with a specialist is recommended if acute liver injury is suspected.

Elevated troponin-I levels and myocarditis has been observed. It is recommended to monitor troponin-I levels before infusion and weekly subsequently for the first month after Elevidys.

**Prior Authorization Information**

**Inpatient**
- For services described in this policy, precertification/preauthorization is **REQUIRED** for all products if the procedure is performed **inpatient**.

**Outpatient**
- For services described in this policy, see below for products where prior authorization might be **required** if the procedure is performed **outpatient**.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Outpatient</th>
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<tbody>
<tr>
<td></td>
<td>*Prior authorization is required.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
<td>*Prior authorization is required.</td>
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<tr>
<td>Medicare HMO Blue(^{SM})</td>
<td>*Prior authorization is required.</td>
</tr>
<tr>
<td>Medicare PPO Blue(^{SM})</td>
<td>*Prior authorization is required.</td>
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</table>
CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS Codes

<table>
<thead>
<tr>
<th>HCPCS codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>J3590</td>
<td>Unclassified biologics</td>
</tr>
<tr>
<td>J3490</td>
<td>Unclassified drugs</td>
</tr>
<tr>
<td>C9399</td>
<td>Unclassified drugs or biologicals</td>
</tr>
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</table>

ICD-10 Diagnosis Code

<table>
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<tr>
<th>ICD-10 Diagnosis Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>G71.01</td>
<td>Duchenne or Becker muscular dystrophy</td>
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SUMMARY

Background

Duchenne Muscular Dystrophy (DMD)
Duchenne muscular dystrophy (DMD) is a progressive, X-linked, degenerative neuromuscular disease that results in disabling muscle weakness and eventually leads to early death. DMD is caused by mutations in the dystrophin gene resulting in reduced or near absence of dystrophin, a protein that helps keep muscle cells intact. The estimated incidence of DMD is 1 in 3500–5000 male births (i.e., 400 to 600 boys per year) with prevalence estimates ranging between 10,000 and 15,000 males. Boys are typically diagnosed at 4-5 years of age. As the disease progresses, muscle weakness and atrophy spread to affect additional muscles of the body. By the early teenage years, patients will typically require a wheelchair and serious life-threatening complications may ultimately develop including cardiomyopathy and respiratory difficulties. DMD mainly affects males and in rare cases may affect females. Although disease severity and life expectancy vary, patients often succumb to the disease in their 20s or 30s because of heart and/or respiratory failure.1-4

Currently, there are two main therapeutic approaches in use for the treatment of DMD. Therapies aimed at improving muscle that target the downstream pathological changes of DMD and therapies aimed at restoring dystrophin function. Pharmacological treatment with corticosteroids, such as prednisone and Emflaza, are the mainstay of DMD treatment strategies because of their beneficial effects for improving motor function and pulmonary function, reducing the risk of scoliosis, delaying the loss of ambulation, and possibly for delaying progression of cardiomyopathy and improving survival. Gene-based therapies that involve exon skipping (Exondys 51, Vyondys 53, Viltepso, Amondys 45) are approved for the treatment of DMD. These therapies increase dystrophin expression, but clinical benefit is still to be established.

Gene Therapy for DMD
The dystrophin gene is one of the largest in the human genome (2.3 million base pairs, over 11,000 of which are for coding). Because of the gene’s size, it is difficult to insert the complete coding DNA sequence for dystrophin into a viral vector. The carrying capacity of AAVs is approximately 4.7 kilobases.
Therefore, rather than use the full dystrophin gene (2200 kb in size), the gene therapy technology uses a smaller, modified gene that produces shortened forms of dystrophin, called micro-dystrophin (3.5-4 kb in size) and mini-dystrophin (6-8 kb in size).

Both micro- and mini-dystrophin have been designed to function like normal dystrophin protein requiring that these smaller treatments are delivered at high doses.

Elevidys is a recombinant gene therapy designed to deliver into the body a gene that leads to production of Elevidys microdystrophin, a shortened protein (138 kDa, compared to the 427 kDa dystrophin protein of normal muscle cells) that contains selected domains of the dystrophin protein present in normal muscle cells.\(^4\)

**Summary of Evidence**

Accelerated approval was primarily based on data from Study 1 and Study 2 described below.

Study 1 is an ongoing multi-center study including:

- Part 1: a 48-week, randomized, double-blind, placebo-controlled period
- Part 2: a 48-week period that began following completion of Part 1. Patients who received placebo during Part 1 were treated with ELEVIDYS, and patients treated with ELEVIDYS during Part 1 received placebo.

The study population consisted of male ambulatory DMD patients (N=41) aged 4 through 7 years with either a confirmed frameshift mutation, or a premature stop codon mutation between exons 18 to 58 in the DMD gene.

All subjects were on a stable dose of corticosteroids for DMD for at least 12 weeks prior to ELEVIDYS infusion. All randomized subjects had baseline anti-AAVrh74 antibody titers <1:400 as determined by an investigational total binding antibody ELISA.

One day prior to treatment with ELEVIDYS or placebo, the subject's background dose of corticosteroid for DMD was increased to at least 1 mg/kg of a corticosteroid (prednisone equivalent) daily and was continued at this level for at least 60 days after the infusion, unless earlier tapering was clinically indicated.

The primary objectives of Study 1 were to evaluate expression of ELEVIDYS micro-dystrophin in skeletal muscle, and to evaluate the effect of ELEVIDYS on the North Star Ambulatory Assessment (NSAA) total score.

Patients were randomized 1:1 to receive either ELEVIDYS (N=20) or placebo (N=21), as a single intravenous infusion via a peripheral limb. Randomization was stratified by age (i.e., aged 4 to 5 years vs. aged 6 to 7 years). In the ELEVIDYS group, eight patients received 1.33 × 10^{14} vg/kg of ELEVIDYS, and 12 patients received lower doses.

The change in NSAA total score was assessed from baseline to Week 48 after infusion of ELEVIDYS or placebo. The difference between the ELEVIDYS and placebo groups was not statistically significant (p=0.37). The least squares (LS) mean changes in NSAA total score from baseline to Week 48 was 1.7 (standard error [SE]: 0.6) points for the ELEVIDYS group and 0.9 (SE: 0.6) points for the placebo group.

Exploratory subgroup analyses showed that for subjects aged 4 through 5 years, the LS mean changes (SE) in NSAA total score from baseline to Week 48 were 4.3 (0.7) points for the ELEVIDYS group, and 1.9 (0.7) points for the placebo group, a numerical advantage for ELEVIDYS. For subjects aged 6 through 7 years, the LS mean changes (SE) in NSAA total score from baseline to Week 48 were -0.2 (0.7) points for the ELEVIDYS group and 0.5 (0.7) points for the placebo group, a numerical disadvantage for ELEVIDYS.
Study 2 is an ongoing, open-label, multi-center study which includes a cohort of 20 ambulatory male DMD subjects aged 4 through 7 years. All 20 subjects have a confirmed frameshift mutation, canonical splice site mutation, or premature stop codon mutation in the DMD gene.

At study entry, 75% of subjects were white with a mean age of 5.81 years (range: 4.38 to 7.94), mean weight of 21.2 kg (range: 15.2 to 33.1), mean NSAA total score of 22.1 points (range: 18 to 26), and mean time to rise from floor of 4.2 seconds (range: 2.4 to 8.2). Subjects received corticosteroids for DMD before infusion. All subjects had baseline anti-AAVrh74 antibodies titers <1:400 as determined by the investigational total binding antibody ELISA and received a single intravenous infusion of $1.33 \times 10^{14}$ vg/kg ELEVIDYS.

The primary objective of the study was to evaluate the effect of ELEVIDYS micro-dystrophin expression as measured by western blot.

### Micro-Dystrophin Expression in Studies 1 and 2 (Western Blot Assay)

<table>
<thead>
<tr>
<th>Western blot (% of ELEVIDYS micro-dystrophin compared to control)</th>
<th>Study 1 (Week 12) Part 1 (n = 6)</th>
<th>Study 1 (Week 12) Part 2 (n=21)</th>
<th>Study 2 (Week 12) Cohort 1 (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline (SD)</td>
<td>43.4 (48.6)</td>
<td>40.7 (32.3)</td>
<td>54.2 (42.6)</td>
</tr>
<tr>
<td>Median change from baseline (Min, Max)</td>
<td>24.3 (1.6, 116.3)</td>
<td>40.8 (0.0, 92.0)</td>
<td>50.6 (4.8, 153.9)</td>
</tr>
</tbody>
</table>

a All patients received $1.33 \times 10^{14}$ vg/kg, as measured by ddPCR
b Muscle biopsies were obtained from the gastrocnemius
c Change from baseline was statistically significant
d Adjusted for muscle content. Control was level of wild-type (normal) dystrophin in normal muscle

### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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### Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

### References